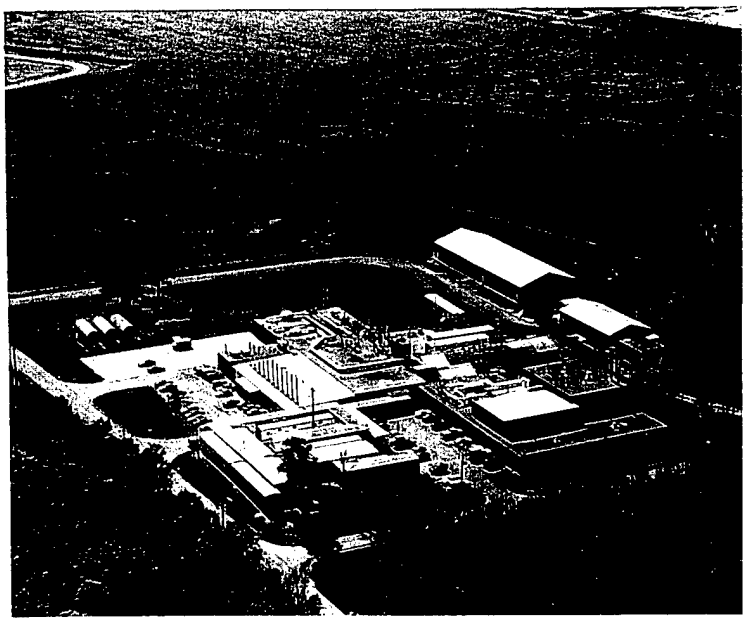
REPORT

FINAL REPORT

Task 97-48: Respiratory Casualty Care Management in the Field Medical Environment



To

U.S. Army Medical Research Institute of Chemical Defense

July, 2000

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FINAL REPORT

Contract No. DAMD 17-89-C-9050
A Medical Research and Evaluation Facility (MREF) and Studies Supporting the Medical Chemical Defense Program

on

Task 97-48: Respiratory Casualty Care Management in the Field Medical Environment

to

U.S. Army Medical Research Institute Of Chemical Defense

July, 2000

by

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Task 97-48: Respiratory Casualty Care Management in the Field Medical Environment

July, 2000

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Award Number: DAMD17-89-C-9050

TITLE: A Medical Research and Evaluation Facility (MREF) and Studies Supporting the Medical Chemical Defense Program

Subtitle: Respiratory Casualty Care Management in the Field Medical Environment

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REPORT DATE: July 2000

TYPE OF REPORT: Final, Task 97-48

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)

2. REPORT DATE
July 2000

3. REPORT TYPE AND DATES COVERED
Final, Task 97-48

4. TITLE AND SUBTITLE
A Medical Research and Evaluation Facility (MREF) and Studies Supporting the Medical Chemical Defense Program

Subtitle: Respiratory Casualty Care Management in the Field Medical Environment

5. FUNDING NUMBERS
DAMD17-89-C-9050

6. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; Distribution unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

Task 97-48 was conducted in two phases: 1) develop a 72-hr anesthetized, ventilated respiratory casualty swine model and 2) assess treatment efficacy of a) 10-15 cm of water positive end expiratory pressure (PEEP) with 45 percent oxygen, b) Ibuprofen (IBU), and c) n-acetyl-cysteine (NAC). The early diagnostic capability for pulmonary edema (PE) using the impedance cardiograph was evaluated in Phase II. Phosgene (CG) was selected as the respiratory insult and exposures ranged from 250 to 1000 mg/m^3 for 10 min. A CG exposure concentration of 450 mg/m^3 over a 10 min exposure (4,500 mg·min/m^3), a challenge estimated to be lethal to 85 percent, was selected for evaluating treatment efficacies. Swine were infused with pentobarbital sodium (~3 mL/hr, 65 mg/mL) to maintain anesthesia. The pigs were paralyzed with vercuronium chloride (2 mg initially then 1 mg hourly) and placed on a ventilator with a tidal volume of 15 mL/kg, an inspiratory:expiratory ratio of 1:1, and a respiratory rate of 15 breaths per min. Statistically no treatment appeared to be consistent in moderating the LCt_{85} CG exposure. PEEP with 45 percent oxygen was not effective in prolonging survival. IBU and NAC increased survival to ~30 hr after exposure ended as opposed to 25 hr after exposure ended for CG only. The impedance cardiograph was inconsistent in the early diagnosis of PE.

14. SUBJECT TERMS
Swine (pigs); Phosgene (CG); prolonged anesthesia (72-hr); anesthetized, ventilated swine model; positive end expiratory pressure (PEEP), Ibuprofen, N-acetyl-cysteine, impedance cardiograph, Pulmonary edema.

15. NUMBER OF PAGES
308

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

EXECUTIVE SUMMARY

One mission of the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD) is to provide medical management techniques for chemical warfare (CW) casualties. The emphasis on research and identification of products particularly relevant to clinical management is identified in the Joint Service Agreement, USA code S-A-304 and in the Medical Chemical Defense Work Breakdown Structure, WBS codes 6.6.1.4.7.7.4. Treatment of CW respiratory casualties has not been thoroughly studied. A respiratory casualty model is needed to evaluate diagnostic equipment and techniques and medical treatment and management of respiratory casualties such as those due to phosgene (CG) exposure. The Medical Research and Evaluation Facility (MREF) at Battelle conducted Task 97-48 to develop a 72-hr anesthetized, ventilated respiratory casualty model, assess the treatment efficacy of positive end expiratory pressure (PEEP) with 45 percent oxygen (O_2), and determine the early diagnostic capability of the impedance cardiograph for pulmonary edema (PE). Two compounds, Ibuprofen (IBU) and N-Acetyl-cysteine (NAC), were added to the treatment efficacy study. The task was designed in two phases. Phase I was the development of the model and the selection of a CG exposure for the second phase. Phase II was the evaluation of the impedance cardiograph and treatment efficacy studies.

Phase I

CG was selected to induce the respiratory insult because of its relevance as an industrial hazard and as a military threat. The pig was selected as the test system because of its similarities in cardiopulmonary physiology, and growth and size of organs to that in human beings. In addition, swine used extensively in cardiopulmonary biomedical research and are readily available.

A 72-hr anesthetized, ventilated swine model was developed. Pigs were catheterized, and infused with lactated Ringer's solution and with pentobarbital sodium (~3 mL/hr, 65 mg/mL) to maintain anesthesia. The animals were paralyzed with vercuronium chloride (2 mg initially then 1 mg hourly) and placed on a ventilator with a tidal volume of 15 mL/kg, an inspiratory:expiratory time ratio of 1:1, and a respiratory rate of 15 breaths per min. Selected physiology, hematology, and clinical chemistry parameters were measured and analyzed.

Clinical chemistries and selected physiological endpoints remained in the normal range or were consistent for an anesthetized animal. Statistical trends were not clinically significant. The 72-hr anesthetized ventilated, swine model developed in Phase I was used in Phase II efficacy studies challenged with a CG exposure concentration of 450 mg/m^3 for 10 min (LCt_{85}) or 10 min of air in control animals.

Phase II

Seven groups, 4 controls and 3 treatments, were evaluated in Phase II. Treatments included PEEP with high (45%) O_2 started shortly after the 10-min CG exposure; a 30 min slow infusion of an IBU 45 mg/kg loading dose administered 30 min after the end of air or CG exposure, followed by 22.5 mg/kg infused every 2 hr for 24 hr after the end of air or CG exposure; and 2 mL of 20 percent NAC administered intratracheally at 30 min and then every 4 hr for 16 hr after the end of exposure. The impedance cardiograph was evaluated over the course of the study for early detection of PE. Animals were exposed to either air or CG targeted at 450 mg/m^3 for 10 min (4,500 mg·min/m^3).

Treatments

Limited evidence of treatment efficacy was noted. Statistically, none of the treatments were consistently effective, across all parameters measured, in moderating the effects of an LCt_{85} CG exposure.

PEEP with high O_2 (45 %): Survival time of CG/PEEP with 45 % O_2 animals (~24 hr) was equivalent to CG/no treatment animals and significantly less than the air/no treatment group (72 hr). There was a suggestion that PEEP treatment mitigated the effect of CG on arterial oxygenation (P_aO_2,) probably due to PEEP forcing O_2 across the alveolar-capillary membrane. Treatment with CG/PEEP was terminated after 4 animals since there was no indication of efficacy.

IBU and NAC: IBU and NAC minimally improved survival time (~33 and ~30 hr, respectively) over CG/no treatment (~25 hr). The NAC treatment groups were stopped when it appeared less effective than IBU animals.

Discriminant analysis: This analysis method was used to determine what measurements/endpoints would be most effective in evaluating the treatments and early indicators of CG intoxication. The key variables identified in the discriminant analysis were: peak blood urea nitrogen (BUN) within first 48 hr, average inspired oxygen during the first 24 hr, peak blood potassium (K) level, average P_aO_2 and arterial carbon dioxide (P_aCO_2) during the first 24 hr, mean expired CO_2, overall average pulse rate, and slope of blood chloride concentration versus time. Of these, BUN, K, P_aO_2, P_aCO_2, expired CO_2, and pulse rate were identified as possible early indicators of the effects of CG exposure. BUN was increased during the first 24 hr. Once the urinary bladder was catheterized and the urine expressed, the BUN returned to a normal range within 24 hr. IBU-treated animals were the exception; BUN levels did not return to baseline for up to 48 hr after exposure. This may be the result of IBU's side effects in an already compromised animal, possibly due to decreased renal blood flow leading to reduced urine output. Average inspired O_2 was a controlled parameter and one of the treatment variables. The inspired O_2 was maintained at about 45 percent for the CG/PEEP with high O_2 group and at about 30 percent in the other treatment groups.

No one treatment consistently moderated the effects of CG exposure across the parameters measured. Peak K levels in the Air/IBU ($p=0.009$) and CG/PEEP ($p=0.007$) groups were significantly greater than that in the Air/no treatment control group, and were marginally different ($p=0.0996$) from the CG/no treatment group. The IBU and NAC treated CG-exposed animals had lower peak K levels (<6 mmol/L) than the CG/no treatment, CG/PEEP, and Air/IBU animals. The mean P_aO_2 in the CG/PEEP group during the first 24 hr was similar to that in the air-exposed groups, but was depressed in the other CG-exposed groups ($p<0.01$). Mean P_aCO_2 during the first 24 hr was greater in the CG/IBU group than in the Air/IBU ($p=0.045$) and Air/no treatment ($p=0.039$) groups. Mean P_aCO_2 for the other CG-exposed groups was increased, but to a lower mean value. A significant group effect was detected for expired CO_2 during the first 24 hr. Pair-wise comparisons, however, did not indicate significant differences between groups when adjusted for multiple comparisons. The CG/IBU mean expired CO_2 was marginally greater than that of the AIR/IBU group ($p=0.069$), while smaller differences were observed between the means of the other groups. No significant differences in the overall average pulse rate were observed among the groups, although the CG/no treatment and CG/IBU mean scores were marginally greater than all other group mean scores. No significant differences among the

group means were observed for the slope of chloride concentration vs. time, but variability was high in the CG-exposed groups. Average slopes in the CG/PEEP, CG/IBU, and CG/NAC groups appear to be somewhat greater on average than those of air-exposed and CG/no treatment animals, although these differences were not statistically nor clinically significant. In the CG/IBU and Air/IBU groups there was some evidence that glucose levels declined when BUN, levels were elevated above the normal range during the first 24-hr on study.

The repeated measures analysis was used to detect potential early indicators of treatment effect. The timecourse variable was statistically significant ($p<0.0001$) for K, P_aO_2, P_aCO_2, BUN, pulse rate, and expired CO_2, which suggests that these variables may be considered early indicators of CG exposure. The effect of exposure/treatment group was statistically significant for K ($p=0.011$) and P_aO_2 ($p<0.0001$), although these differences are not necessarily indicative of treatment efficacy. K levels in the Air/IBU and CG/PEEP groups became elevated in the first 8 hr, while the K levels for other groups remained within the normal range in surviving animals. For P_aO_2, average levels for CG-exposed groups were lower than those in air-exposed groups, but the IBU and NAC treatments do not appear to moderate this effect. The interaction between exposure/treatment group and study timecourse was statistically significant ($p<0.001$) for K, P_aO_2, expired CO_2, and pulse rate, and for BUN ($p=0.004$), which indicates that the average response varied inconsistently among the treatments over the early timepoints. BUN should not be considered an early indicator of CG exposure since BUN increase was the result of urine retention until the bladder was catheterized.

Impedance Cardiograph:

In this model, the impedance cardiograph was not an effective instrument for detecting early PE. This may be because of anatomical differences between swine and human beings. Greater variability in the slope of impedance versus time was noted among animals that died compared to those that survived, although the effect did not appear to be treatment-related.

CONCLUSION

A respiratory casualty care model has been developed and can be used to evaluate treatment protocols, therapy compounds, and equipment for diagnosis, analysis or therapy of a respiratory casualty. There is limited evidence of treatment efficacy and is based predominantly on survival time. Statistically, none of the treatments appeared to be consistently effective in moderating the effects of a LCt_{85} CG exposure. PEEP with high O2 was not effective. The swine respiratory casualty care model may not be a good model for evaluating the impedance cardiograph.

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POSITIVE END EXPIRATORY PRESSURE (PEEP), IBUPROFEN (IBU), AND N-ACETYLCYSTEINE (NAC) EFFICACY STUDY IN SWINE EXPOSED TO PHOSGENE

TASK 97-48 PHASE I

DEVELOPMENT OF A PROLONGED ANESTHESIA (72 HR), VENTILATED SWINE, RESPIRATORY-INSULT MODEL

1.0 INTRODUCTION

Exposure to a wide variety of chemicals may occur due to industrial accidents, battlefield conditions, or terrorist actions. Treatment of chemical warfare (CW) respiratory casualities has not been thoroughly studied. There is a critical need for development of a model to evaluate potential avenues of therapy for respiratory casualties such as those due to phosgene (CG) exposure. One mission of the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD) is to provide medical management techniques for CW casualties. The emphasis on research and identification of products particularly relevant to clinical management is identified in the Joint Service Agreement, USA code S-A-304 and in the Medical Chemical Defense Work Breakdown Structure, WBS codes 6,6.1.4,7,7.4.

Areas of concern for the respiratory casualty include pulmonary edema (PE), hypoxia, hypotension, excess secretions, bronchospasms, right heart failure, and infection.[1-10] Clinical concerns with choking agents, such as CG, are the same as those for the respiratory casualty. CG irritates the tracheobronchial tree and produces pulmonary edema.[3] Although choking agents are very effectively excluded by a properly worn and maintained gas mask, substantial toxicity may occur before the individual becomes aware of an exposure and dons a mask. The earliest evidence of a toxic exposure to CG may be tachypnea or dyspnea. This is a serious problem because, even after lethal exposures, abnormal lung sounds, radiologic evidence of infiltrate, blood gas abnormalities, and other evidence of impending pulmonary edema may not appear until two to six hr after exposure.[1-10]

A respiratory casualty model is needed to evaluate diagnostic equipment and techniques and medical treatment and management of respiratory casualties. CG was selected to induce the respiratory insult because of its relevance as an industrial hazard and as a military threat. The pig was selected as the model because of its similarities in cardio-pulmonary physiology to that of human beings, similar growth and size of organs to that in human beings, ready availability, and extensive history in cardio-pulmonary biomedical research.[11-12]

1.1 Objectives

The main objectives of Phase I were to: 1) develop a 72-hr anesthetized, ventilated swine model, and measure selected physiological and clinical chemistry endpoints; 2) assess the clinical status of animals over 72 hr and identify techniques and endpoints for assessment; and 3) determine endpoints and sampling times for use in Phase II efficacy experiments. In addition, the impedence cardiograph was evaluated for detection of early onset of PE. The Phase I model and data collected were to be used in Phase II to evaluate the efficacy of medical treatments and management of CG casualties, including positive pressure ventilation with high oxygen concentration, ibuprofen (IBU), and N-acetylcysteine (NAC) therapies.

2.0 MATERIALS AND METHODS:

2.1 Study Design

Phase I was divided into two parts: 1) developing the 72-hr anesthetized, ventilated swine model; and 2) determining the CG exposure parameters to be used in Phase II. The impedance cardiograph was used in both parts to assess the early diagnostic capabilities of the impedance cardiograph. Also included in Phase I were equipment installation and demonstration of adequate performance, technician training, writing of Standard Operating Procedures (SOPs), and determination of the CG exposure-pulmonary response over 72 hr. Table 1 lists the monitoring equipment used and the parameters measured.

Table 1. Monitoring Equipment and the Parameters Measured by Each Unit

Instrument Name	Manufacturer	Parameters Measured/Use
Protocol Propaq	Protocol Systems, Inc. Beaverton, OR	Heart Rate (beats per min) Blood Pressure – Systolic, Diastolic, and mean pressure (mm Hg) Body Temperature (degrees F)
5250 Respiratory Gas Monitor	Ohmeda Louisville, CO	Inspired O_2 (mm Hg), Expired CO_2 (mm Hg), Oxygen saturation of capillary blood (SO_2, %), pulse rate (beats per min), and respiratory rate (breaths per min)
Bear® 33 Volume Ventilator with humidifier	Bear Medical Systems, Inc. Palm Springs, CA	Set at 15 breaths per min for study. 1:1 inspiratory:expiratory ratio Tidal Volume = 15 mL/kg body weight
I-STAT Systems	I-STAT Corporation Waukesha, WI	Arterial blood pH, partial pressure of oxygen (P_aO_2, mm Hg), partial pressure of carbon dioxide (P_aCO_2, mm Hg), bicarbonate ion (HCO_3, mmol/L), total carbon dioxide (TCO_2, mmol/L), SO_2 (%), base excess (BE, mmol/L), anion gap (An Gap, mmol/L), hemoglobin (Hb, g/dl), hematocrit (hct, %), sodium (Na, mmol/L), potassium (K, mmol/L), chloride (Cl, mmol/L), blood urea nitrogen (BUN, mg/dl), and glucose (Glu, mg/dl)
Minnesota Impedance Cardiograph	Surcom, Inc. Minneopolis, MN	Impedance of thoracic cavity measured in ohms.
MinXray 803	MinXray, Inc. Northbrook, IL	Lateral and ventrodorsal thoracic radiographs initially. Lateral thoracic radiographs for study
Companion 590 Oxygen Concentrator	Puritan/ Bennett Distributed by Mallincrot Chicago, IL	Concentrates room air oxygen to desired level for administration via ventilator.
Bair® Hugger Blanket	Augustine Medical, Inc. Eden Prairie, MN	Maintain animal body temperature between 101 and 104 F.

2.2 Test System

Eighteen castrated male and three boar, Yorkshire purebred and crossbred, swine (*Sus scrofa*) weighing approximately 19 kg (range of 16-24 kg) when placed on study, were used to develop the 72-hr anesthetized, ventilated swine model and to determine the CG exposure parameters. Personnel assisting in the study were trained on the equipment prior to initiation and during the study.

Isler Genetics, Inc.(Prospect, OH), a specific pathogen free (SPF) facility and an animal source approved by Battelle's Attending Veterinarian, provided the animals used on study. Animals were quarantined in-house for 7 days prior to placement on study. Animals were identified by the producer's ear-notch system. Feed was provided twice a day at a total of approximately 0.6 to 1.5 kg per day. Animals were weaned from the producer's ration to a laboratory swine grower ration (PMI Feeds, Inc., St. Louis, MO). Feed was removed approximately 17 hr prior to initiating anesthesia. Water from Battelle's West Jefferson wells was supplied *ad libitum* from an automated Edstrom (Waterford, WI) watering system. No contaminants that would affect the results of the study are known to be present in the feed or water.

Animals were pair-housed in a 4 ft by 4 ft nursery pen (Palco, Inc., Belleplaine, IA) during quarantine. Fluorescent lighting was used with a light/dark cycle of approximately 12 hr each per day. Air temperature in swine rooms was maintained between approximately 16 to 27 C.[13] The room temperature was maintained at the upper end of the range following receipt of animals and gradually reduced over time to approximately 18.3 C for animals maintained greater than one week. Relative humidity in animal rooms was maintained between approximately 30 and 70 percent.

Animals at Battelle are cared for in accordance with the guidelines set forth in the "Guide for the Care and Use of Laboratory Animals" (National Academy of Sciences, 1996), and/or in the regulations and standards as promulgated by the Agricultural Research Service, United States Department of Agriculture (USDA), pursuant to the Laboratory Animal Welfare Act of August 24, 1966, as amended.(13) On January 31, 1978, Battelle's Columbus Division received full accreditation of its animal care program and facilities from the American Association for Accreditation of Laboratory Animal Care (AAALAC). Battelle's full accreditation status has

been renewed after every inspection since the original accreditation. The MREF is a part of the Battelle facilities granted full accreditation.

2.3 General Procedures

Equipment adjustments were performed by or under the direction of a staff veterinarian, Contracting Officer's Representative (COR), or Study Director. During the conduct of this phase, a veterinarian was present with the animal for most of the 72 hr. LTC Keith Vesely, USA,VC was present during the day (~12 hr) and Dr. Frances Reid worked nights (~12 hr). When LTC Vesely was transferred to another assignment, a Battelle staff veterinarian (Dr. Robert Hunt or Dr. Carl Olson) was on call for the day shift. Dr. Reid continued as the Study Director and veterinarian at night for the course of the task. Table B.1.a and Table B.1.b (Attachment B) present normal values for physiological parameters measured. [14, 15, 16] Table B.2, entitled "Selected Parameters with Acceptable Ranges and Adjustments," in Attachment B presents a brief description of conditions and adjustments for selected physiological parameters that were recommended during the initial model development (first 5 animals). Minimal adjustments were necessary for the anesthetized, ventilated swine model. Dr. Reid, in consultation with the USAMRICD COR (LTC Richard Stotts) and Technical Point of Contact (TPOC; Dr. Alfred Sciuto) established settings for the asterisk-identified parameters (such as fluid therapy, respiratory rate, and percent inspired oxygen).

2.3.1 Preparations, Anesthesia, and Surgery

Animals were weighed prior to preanesthetic administration. Atropine (0.05 mg/kg; AMVET Scientific Products, Yaphank, NY) was injected intramuscularly (im) in the first animal to counteract the excessive secretory response and increased peristalsis effect expected from the anesthetic. Since it appeared that the atropine thickened mucus secretions and created a plug that blocked the endotracheal tube, resulting in the first animal's early death, atropine was not given to succeeding animals.

Five mL of xylazine hydrochloride (100 mg/mL, Ben Venue Laboratories Inc., Bedford, OH) was used to reconstitute the 250 mg of tiletamine and 250 mg zolazepam combination of Telazol® (Fort Dodge, Fort Dodge, IA). This Telazol®/xylazine combination was administered

im at 0.044 mL/Kg as a preanesthetic. After approximately 10 min, the animal was moved into the surgery room and 3 percent isoflurane (Forane®; Ohmeda PPD, Inc., Liberty Corner, NJ) was delivered by an Ohio Vaporizer (Surgivet/Anesco, Waukesha, WI), mounted on a Matrix anesthetic machine (Matrix Medical, distributed by Butler, Columbus, OH), via mask. Cetecaine® (J. A. Webster, Sterling, MA) was sprayed on the larynx to prevent spasms. A size 5 or 6 French (Fr) endotracheal tube (Butler, Columbus, OH) was inserted, the cuff inflated, and the animal placed on approximately 2 percent isoflurane carried by 1 liter per min oxygen (O_2; Paxair, Columbus, OH). A surgical plane of anesthesia was established before placement of femoral artery and vein catheters. Catheter placement initially took an average of 1.4 hr. This time was later reduced to 0.75-1 hr. The arterial catheter was generally a 7 Fr (range of 5-8 Fr; Arrow International, Reading, PA) and the venous catheter an 8 Fr.

After skin closure, lactated Ringer's solution (Abbott Laboratories, North Chicago, IL) and pentobarbital Na (65 mg/mL; Butler, Columbus, OH) infusions were initiated through the femoral vein catheter. Animals were transitioned from the isoflurane to a slow infusion (rate ~3 mL/hr) pentobarbital anesthesia using incremental boluses (0.5 to 2.0 mL) as indicated. Initially, animals were transitioned from isoflurane over 30 min. This time was later reduced to an average of 12 min. During this change in anesthetic agent, the animal was placed on room air for at least 10 min before being moved to the exposure laboratory. Pentobarbital Na infusion was maintained for 72 hr following exposure or until death of the animal. During anesthesia, presence of a palpebral reflex, shivering, increasing heart rate, increasing blood pressure, or a combination of these signs was used as an indication to administer additional pentobarbital.

2.3.2 Fluid Therapy

Initially, sterile physiological saline (Phoenix Scientific, St. Joseph, MO) was alternated with Dexalyte (Butler, Columbus, OH) to provide an essential energy source and electrolytes. Anesthesiologists and technical personnel of intravenous fluid manufacturers indicated that sterile lactated Ringer's would be adequate for 72 hr of anesthesia. In the second animal, sterile lactated Ringer's solution was infused at a rate of 45 mL/hr, and this solution only was used for the remainder of the study.

2.3.3 Physiologic/Biomechanical Monitoring

Normal values for physiologic parameters were compiled from several sources and are presented in Tables B.1.a and B.1.b of Attachment B.[14, 15, 16] Each animal was connected to a Protocol Propaq for measuring the electrocardiogram (ECG), body temperature, and arterial blood pressure (BP_a).

The desired tidal volume for each animal was determined by multiplying 15 mL/kg times the body weight in kg.[15-19] The tidal volume on the Bear® 33 Volume Ventilator was then set at the nearest whole number. The expiratory-inspiratory ratio was set at 1:1. Initially, the respiratory rate (RR) was adjusted as needed to target a $P_aO_2 \geq 80$ mm Hg and a P_aCO_2 between 35 and 45 mm Hg. Before phosgene exposures began, the Study Director in consultation with the COR and TPOC established the RR for the volume ventilator at 15 breaths per min (brpm), as indicated by the anesthetized, ventilated swine data and as recommended in the *Textbook of Critical Care*, 3rd Ed. (Shoemaker, et al., 1995).

Of the first seven animals, six were placed on the ventilator with humidifier and injected iv with Norcuron® (1 mg vercuronium chloride/mL; Organon, West Orange, NJ) before exposure. Initially, 2 mL of Norcuron® were given and then 1 mL at hourly intervals thereafter. If the animal resisted the ventilator, then up to 2 mL Norcuron® were administered and/or the anesthetic flow rate was adjusted.

The Ohmeda 5250 Respiratory Gas Monitor was connected to the ventilator tubing and used to monitor inspired oxygen (IO_2), expired carbon dioxide (ECO_2), and RR. The oxygen saturation (SO_2) sensor was attached to the lower lip because readings measured from the ear or between the digits were less accurate or not detectable. The O_2 concentrator was used to maintain IO_2 at about 30 percent in control, anesthetized animals. Early in model development, the oxygen concentrator was used sporadically in an attempt to raise the P_aO_2 above 90 mm Hg (evaluated using the I-STAT on arterial blood) or peripheral SO_2 above 60 mm Hg (evaluated using pulse oximeter).

Arterial blood sampling was accomplished prior to exposure, generally just before moving the animal into the chemical fume hood. Blood samples were drawn ~ 1 hr after exposure and every 4 hr thereafter, and/or as directed by the study director, a staff veterinarian or the COR. The I-STAT Portable Clinical Analyzer required approximately 3-4 drops of

heparinized blood (heparin, 1000 units/mL; Elkins-Sinn, Inc., Cherry Hill, NJ) per cartridge to analyze clinical chemistry parameters and arterial blood gases. Two cartridges (G3+ and EC8+) were used to analyze the following parameters: arterial blood pH, P_aO_2, partial pressure of carbon dioxide (P_aCO_2), bicarbonate ion (HCO_3), total carbon dioxide (TCO_2), SO_2, base excess (BE), anion gap (An Gap), hemoglobin (Hb), hematocrit (hct), sodium (Na), potassium (K), chloride (Cl), blood urea nitrogen (BUN), and glucose (Glu).

The Bair Hugger® Warming Blanket was used to maintain the body temperature at about 59.2 C. Body temperature was monitored using a rectal probe connected to the Protocol Propaq. Towels and blankets were used in conjunction with the warming blanket to maintain the pig's body temperature between 38.3 and 40.0 C.

A MinXray 803 was used to detect radiographic evidence of PE following CG exposure. A technique chart was created and used as a guide for amperage and time settings. Initially, ventro-dorsal and lateral views were taken immediately after exposure, at 1 hr and at every 4 hr after CG exposure. The peak kilovoltage of the unit, however, was insufficient to obtain diagnostic quality radiographs. If the time was increased, too much movement was evident on the radiograph. Evidence of pulmonary edema could be observed on the radiographs, however the sharp, distinct quality required for early diagnosis was not obtained. Discussions held by the Study Director with a radiologist, the COR, and the TPOC resulted in a reduction in the frequency of radiographic exposures, and subsequently only lateral views were taken. The animals used on this task were relatively consistent in size and weight, and their chest measurements were also consistent, with thoracic cavity lateral depth measurements between 13 and 15 cm.

The Minnesota Impedance Cardiograph was used to measure in ohms the impedance across the thoracic cavity. Measurements using the impedance cardiograph were initiated on the fifth animal of Phase I. This animal was removed from the hood following exposure and bands were placed - one behind the ears, the second no closer than ~3 cm to the first band (caudal neck), the third around the caudal sternum (xiphoid process), and the fourth band anterior to the umbilicus, but no closer than 3 cm to the third band. Measurements initially were collected hourly. Since the equipment appeared to take a few hr to stabilize despite a prolonged warm-up, measurements were taken every 20 min for 2 hr, then hourly thereafter.

2.3.4 Other Routine Procedures

Animals initially were rotated from side to side every 4 hr. The first animal was euthanatized within 23 hr of being anesthetized due to formation of a mucous plug in the endotracheal tube. Atropine was not administered, and side to side rotation was accomplished every 3 hr with the second animal. The second pig survived for 37 hr before succumbing to a mucous plug blocking the endotracheal tube, similar to that which occurred with the first animal. The time interval between rotations was maintained between 3 and 4 hr, and aspirations of the endotracheal tube were performed more frequently thereafter. The urinary bladder was expressed manually, as needed, with the first 3 animals. The third animal survived more than 72 hr although the urinary bladder had ruptured.

Intensive care nursing consultants were contacted and they came to the facility to observe procedures over the first 4-6 hr (included surgery). Consultation with Ms. Linda Swearingin of Interim Health Care led to the training of technical staff on intensive care procedures routinely used on human patients. Animals were alternated from left side to right side, to left side, etc. every two hr. Tracheal aspirations were accomplished hourly with ~ 0.5-1 mL of sterile physiological saline being administered down the endotracheal tube prior to aspirating. A prepubic urinary catheterization procedure used in human patients was presented as a means to express the urine. Approximately 6-12 hr after the animal was placed on fluids, the urinary catheter was placed. The time fluctuated depending upon when the bladder was large enough to be palpated and held in place. A Foley (12 Fr; Butler, Columbus, OH) urinary catheter was inserted into the urinary bladder using a stainless steel trocar developed by the LTC Stotts. The placement site was prepared by three repetitions of alternating Betadine® scrubs with sterile water rinses of the lower left abdominal quadrant. An incision was made with a number 10 blade through the skin and into the subcutaneous tissue or abdominal muscle ~ 2.5-4 cm left of the ventral midline and between the last two teats. The trocar with the Foley catheter was then placed into the opening. A technician pressed the bladder toward the opening. With the bladder held firmly in place, the trocar was pushed through the abdominal wall and into the bladder. The Foley catheter was inserted into the bladder and the balloon inflated prior to releasing the urinary bladder. The trocar then was secured to the catheter. A Betadine® swab was used to clean the area around the catheter, and a purse-string suture was placed around the catheter to secure it. A

tube was connected to the catheter and placed into a collection bottle to monitor urine output. Animals that survived 72 hr were euthanatized using a concentrated pentobarbital Na solution injected i.v.[20]

Dr. Alfred M. Sciuto replaced LTC Keith Vesely following LTC Vesely's reassignment. Dr. Sciuto recommended the initial CG exposure and the use of wet-to-dry lung weight ratios as a measure of PE. The Study Director included this measurement beginning with animal 11. Upon necropsy, each lung lobe (right, left and accessory) was separated from the trachea and weighed. The accessory lobe was divided in half, with one half being placed in buffered formalin for histopathology and the other half weighed and then placed into a drying oven for 8 days. After 8 days, the dry weight was taken and the difference was the weight of fluid originally in the tissue. Each right and left lobe was subdivided into half and each half was subdivided into thirds and labeled according to the lung map in Figure B.1. (Attachment B). Half of these tissue sections were placed in buffered formalin for histopathology and half were placed in the oven for wet to dry weight determinations. The lung sections were alternated between histopathology and wet to dry weight determinations.

2.4 Phosgene Exposures

Seven pigs were used to develop a 72-hr anesthetized, ventilated model. An eighth pig was exposed to oleic acid to observe PE development and equipment responses. Phosgene exposures began after the eighth animal. Generally, each animal was in the exposure laboratory for 1 to 1.5 hr before exposure was conducted. Ten min air or CG exposures were accomplished using a Harvard Ventilator Model 613 (Harvard Apparatus, Holliston, MA). The system design and the results of all CG exposures (Phases I and II) are described in the Phosgene Exposure System Report, Attachment C. Summary tables of anesthesia (Table E.1) and CG exposures (Table E.2) with survival times are present in Attachment E.

Table 2 presents the group definitions including the total CG exposure concentration ranges per group (total CG exposure concentration = CG exposure concentration • 10 min).

Table 2. Phosgene Exposure Concentrations and Group Definitions

Group	Animal ID	CG – Exposure mg/m^3 · min)
Anesthesia	98-105-3, 98-23-4, 98-24-4, 98-327-6, 98-345-5, 98-45-3†, and 98-37-3	Air
Control *	98-110-2, 98-236-6 and 98-23-4	Air
Low	98-51-3, and 98-60-2	2450 to 3300 CG
Medium	98-55-1, 98-33-3, 98-104-6, 98-18-5, 98-213-1 and 98-232-2	3700 to 4500 CG
High	98-50-7, 98-48-6, and 98-116-3	4900 to 5600 CG

Animals were exposed to 10 minutes to either CG (vary concentrations in an up-down design) or breathable air. Phosgene target exposures of 10,000; 5,500; 5,000 (3 animals at this exposure) 4,500; 4,250 (2 animals); 3,750 (2 animals); 3,250; and 2,500 mg·min/m^3 were used to investigate the CG exposure – lethality relationship. At 2,500 and 3,250 mg·min/m^3 CG exposures, animals survived for 72 hr but had PE. At the 4,250 and 3,750 mg·min/m^3 CG exposures, one of two animals at each level survived for 72 hr and the remaining animals died within 24 hr, but all had PE. Following 10,000; 5,500; 5,000; and 4,500 mg·min/m^3 CG exposures, animals died between 10 min and 24 hr (generally 4 to 20.6 hr). One pig was exposed to 5,000 mg·min/m^3 and was given 300 mg/kg ibuprofen in a treatment pilot study, but the animal died within 5 hr. Another pig was exposed to 4,500 mg·min/m^3 CG and given 10-15 cm of water positive end expiratory pressure (PEEP) with 45 percent oxygen treatment; the animal survived for 14 hr.

2.5 Statistics

The statistics report for Phase I in Attachment D presents a descriptive analysis of the data. The trends identified in this report may not be borne out by statistical hypothesis tests, nor are they necessarily of clinical importance. The clinical chemistry and hematology parameters

evaluated in Phase I experiments were Na, K, Cl, BUN, Glu, arterial blood pH, P_aCO_2, P_aO_2, HCO_3, TCO_2, SO_2, BE, An Gap, Hb, and hct. Physiologic endpoints evaluated in this experiment were expired CO_2, inspired O_2, SO_2, pulse rate (PR), RR, impedance of the thoracic cavity (IMP), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP). Heart rate (HR) was added to the data collection list late in the phosgene exposure evaluation phase. The pulse oximetry connection was difficult to maintain, especially after the side-to-side rotation rate was increased to every 2 hr. This was resolved by using the lip and by more frequently replacing and resetting the oximeter probe. The HR data collected from the Protocol Propaq® served as a check for the pulse oximetry readings.

Summary data tables in the Attachment D Statistics Report display the number of observations (n), mean scores and associated standard errors for blood chemistry, hematology, and physiology parameters. In addition, means with standard error bars are displayed graphically. Normal ranges for several parameters were obtained from published data.[14-17]

3.0 RESULTS

Seven animals were used to develop the procedures for the care and maintenance of a 72-hr anesthetized, ventilated swine model. Problems encountered during the development phase are discussed below. One animal was administered oleic acid to induce PE to observe equipment and animal responses. The impedance cardiograph was attached to observe the response to PE. Thirteen animals were used to determine the CG exposure-lethality response. J.R. Keeler *et al.*, in 1990 reported CG exposure data in sheep that was used to select a starting exposure of 12,000 mg·min/m^3 (1,200 mg/m^3 for 10 min). Consultation with Dr. Alfred M. Sciuto, USAMRICD TPOC after Major Vesely was transferred, resulted in the selection of an initial CG exposure of 10,000 mg·min/m^3 (1,000 mg/m^3 for 10 min) for Phase I.

3.1. 72-hr Anesthetized, Ventilated Swine Model

3.1.1 Anesthesia

Several animals ceased breathing during the weaning from isoflurane anesthesia and shortly after the start of administration of pentobarbital. This occurred in the first six animals with decreasing severity. Ventilation was maintained using an ambu bag to administer room air or oxygen at 1 breath every 5 sec until normal respiration resumed (usually within 35 minutes) or the animal was placed on the ventilator. Cardiac slowing or arrest occurred in several animals during respiratory arrest. Chest compressions were performed until a heart beat was re-established.

3.1.2 Monitoring Equipment

Some monitoring equipment failed during initial set-up. The I-STAT did not function on the first animal since software upgrade had not been performed prior to shipment of the instrument to Battelle. The unit was returned to the manufacturer for repair and upgrade. The respiratory gas analysis equipment was in use by the third animal. The impendance cardiograph was in use by the fifth animal. Difficulties with heart rate data collection were related to the multiple side-to-side rotation and to placement of leads. The pig, being a deep-chested animal, allowed rotation of the heart within the body cavity when the animal was turned. Single placement of the leads on an animal for an optimal electrocardiograph was not feasible. The leads needed to be repositioned periodically, which for some animals was every time it was turned. The decision was made to optimize the lead placement when they were first put on and to collect data from both the Protocol Propaq® and pulse oximetry probe. If the data collected were similar, the leads were properly placed and the data acceptable. If the HR was different than the PR, a technician manually evaluated the animal and documented the correct value. HR and PR differences were related to frequent change in animal positioning and different methods of data collection.

3.1.3 Catheter Placement

Early in model development, there was difficulty in isolating vessels and placing the catheters (surgical procedure ~ 3 hr). The catheters originally on hand were larger (8-10 Fr) than the arterial vessel. Technicians began training as surgical assistants and after assisting on up to four animals, a technician could place the catheters under veterinary surgeon guidance.

3.1.4 Urinary Bladder Catheter Placement

Adequately supporting the bladder to receive the trocar was difficult at times. The sharpness of the trocar was important. If it was too dull, it was difficult to puncture the abdominal wall and enter the bladder. If the trocar was too sharp, the puncture could result in tears in the bladder wall and/or damage to other organs.

3.1.5 Right-Left-Right Continual Rotation

Initially, animals were rotated from side to side approximately every 4 hr. Necropsy of the first animal indicated that atelecteses and congestion were more severe on the side that the animal last rested on. Side-to-side rotation was performed every 3 hr in the next animal, then every 2 hr for the remainder of the animals.

3.1.6 Aspiration

The first two experiments ended with the air exposed animals surviving for only 22.5 hr and 37 hr, respectively. Mucous plugs obliterated the endotracheal tubes in these animals. Attempts to increase the humidity in the ventilator system met with limited success. This prompted consultation with intensive care nurses.

3.1.7 Intensive Care Nursing Consultants

Intensive care and pediatric intensive care nurses were consulted after the loss of the first two animals. Ms. Linda Swearingen and Ms. Patty Groover discussed intensive care techniques, including ventilator and humidifier care, aspirations, and prepubic urinary catheterization, and gave helpful tips on the equipment being used. This resulted in a change to hourly aspirations

using a 0.5-1.0 mL sterile saline wash prior to aspirating for ~8 sec and catheterization of the bladder by a left lower quadrant puncture with a trocar.

3.1.8 Statistics of Anesthesia Data

In Attachment D, Tables 1a, 1b, and 1c present summary statistics for clinical chemistry and hematology endpoints for the anesthesia group, as defined in the Phase I Statistical Report. Figures 1a through 1f display this information graphically. Data were within the normal range. In Table 2, the Anesthesia group identifies the animals used for the analysis.

The following observations were made but were not considered clinically significant. As shown in Table 1a, standard errors for Cl, BUN, and Glu were high, indicating that inter-animal variability was large. P_aO_2 levels increased from a clinically low mean value to within the normal range (80-110 mm Hg) by the end of the experiment. Standard errors were relatively high, as shown in Table 1b and Figure 1c. P_aO_2 was low presumably due to the effect of pentobarbital slowing respiration,. The blood pH levels rose during the first 4 hr and then remained fairly stable in the upper normal range (7.35-7.45). P_aCO_2 declined during the first few hr and then stabilized. TCO_2 and HCO_3 levels fluctuated within the normal range throughout the experiment, but no trends were observed (Figure 1d). SO_2 levels were > 90 percent during the experiment. Na and Cl levels rose slightly (about 140 mmol Na/L and about 112 mmol Cl/L) within the normal range (135-150 mmol/L, 88-115 mmol/L, respectively) and then remained relatively stable. Potassium levels fluctuated within the normal range (3.5-5.5 mmol/L), but did not exhibit any trend over time. Both BUN and glucose levels rose and then fell (Figure 1b). BUN more than doubled (mean of 27 mg/dL at 24 and 28 hr; normal 8-24 mg/dL) during the first 32 hr, and then returned to more normal values in the next 32 hr. This was not deemed clinically significant and probably reflected retention of urine prior to bladder expression. Base excess levels in Table 1c and Figure 1e exhibited relatively large variability. Hemoglobin and anion gap levels fluctuated about the low normal range (10-16 g/dl and 10-25 mmol/L, respectively) during the 72-hr period. Hematocrit levels rose slightly around 48 hr, but otherwise fluctuated around the baseline level. The hematocrit readings for these animals were routinely lower than that reported as the normal range.

Tables 2a and 2b in Attachment D present the descriptive statistics for physiologic endpoints of the group. Figures 2a through 2c display this information graphically. As indicated in Tables 2a and 2b, PR, systolic blood pressure, diastolic blood pressure, and mean blood pressure exhibited great animal-to-animal variability. Figure 2a indicates that expired CO_2 declined and inspired O_2 increased over time. Both systolic (mean 120 mm Hg) and diastolic (mean 77 mm Hg) blood pressure increased within the normal range (100-160 mm Hg and 60-100 mm Hg, respectively) around 48 hr (Figure 2b) and then returned to baseline levels. Mean BP (Figure 2c) showed the same trend. PR increased within the normal range (70-120 beats per min) during the first 32 hr, then declined to levels below baseline but within the normal range. RR was mechanically controlled.

3.2 Oleic Acid Exposure

One animal was exposed to oleic acid to induce PE for training of technicians and to demonstrate animal and equipment responses to the developing edema. Data were collected, but analyses of these data were not performed.

3.3 Anesthesia and Phosgene Data

Thirteen animals were exposed to CG to select a dosing regimen to be used in Phase II efficacy experiments. The phosgene/air exposure system used is described in Attachment C. Phase I anesthesia and CG exposure tables are located in Attachment E. Table 2 above defines and identifies the groups and animals used in these analyses. Data from rodent and sheep exposures served as a guideline in selecting the first exposure.[21-25] In a discussion with Dr. Sciuto, a decision was made to expose the first animal to 10,000 mg·min/m^3. The first animal died shortly after the exposure was completed. A second animal was exposed at 2,500 mg·min/m^3 and lived for the 72-hr observation period. This animal resolved the PE without any therapy. A modified up-down experimental design was used to estimate an exposure at which animals would survive between 24 and 48 hr.

Tables 3a, 3b, and 3c of Attachment D present the descriptive statistics of clinical chemistry and hematology endpoints for control and CG-exposed animals as defined in the statistical report in Attachment D. Figures 3a through 3o graphically display this information.

Sodium levels (Figure 3a) remained within the normal range (135-150 mmol/L) in control and CG-exposed groups. Any trends within this range were not clinically significant. Potassium (Figure 3b) and BUN for all groups increased over the first 8 hr, or until death, before returning to baseline levels in surviving animals, except for BUN in the low-exposure CG group. In this low CG exposure group, BUN levels increased to a high level (20.5 mg/dL) at 52 hr before decreasing to a baseline level (13 mg/dL) at 68 hr, and then increasing again prior to euthanasia (Figure 3d). Chloride levels (Figure 3c) in all groups followed a trend to increase to an upper normal range over the 72-hr period. The Cl level did increase to a value of 125 mmol/L in one medium-level CG exposure animal at ~52 hr. Glucose levels (Figure 3e) generally fluctuated within the normal range (82 to150 mg/dL) throughout the 72-hr observation period in control, low-, and medium-CG exposure animals. In the high CG exposure group, Glu declined to ~60 mg/dL within 4 to 8 hr, then increased before death. Baseline whole blood pH values (Figure 3f) of 7.51 were measured in all groups and were above the reported normal mean of 7.39 in swine. The pH in the high CG exposure animals showed a steady decline until death (pH 7.33). The pH in the survivors of the medium CG exposure group declined slightly (pH 7.43) over the first 8 hr, but returned to baseline values by 20 hr. A mean whole blood pH of 7.33 was measured in animals near death (3 from high- and 3 from medium- CG exposure groups). The pH in the low CG exposure group showed a similar trend, but remained within the normal range and returned to baseline values by 12 hr. P_aCO_2 (Figure 3g) increased until death (56 mm Hg, SE = 7.7, n = 6) in high-CG exposed animals (61.7 mm Hg, SE =10.7, n=3), and in non-survivors in the medium-CG exposed group. In medium-CG exposure animals that survived, P_aCO_2 increased during the first 16 hr and then returned to baseline. P_aCO_2 remained at baseline levels for air control and low-CG exposure animals. P_aO_2 (Figure 3h) abruptly decreased to 48 mm Hg prior to death of animals in the high-CG exposure group. In 72 hr survivors of the medium-CG exposure group, P_aO_2 levels declined over the first 12 hr (to 68 mm Hg) and then gradually increased to baseline values (~112 mm Hg). P_aO_2 levels in the control and low-CG exposure groups generally oscillated within the normal range (80-110 mm Hg) throughout the 72-hr study period. In the high-CG exposure group, HCO_3 (Figure 3i) and total CO_2 (Figure 3j) levels (max at 8 hr of 31.3 and 33.8 mmol/L, respectively) tended to increase until death, while low and medium groups showed a decline over time. SO_2 (Figure 3k)

in arterial blood (measured by I-STAT) decreased abruptly between 4 and 8 hr in the high-CG exposure group, and remained relatively stable within the normal range (> 90 percent) for all other groups. During the 8-16 hr period, the SO_2 for the medium-CG exposure group declined to the upper 80 percent range. Base excess (Figure 3l) fluctuated with a maximum value of 8.3 at 4 hr in the high-CG exposure group and declined over the 72-hr period in other groups, although levels were at peak in the low-CG exposure group at 4 hr. Anion gap (Figure 3m) for the high-CG exposure group declined at 4 hr, but returned to baseline by the time of death. Blood collection time near the time of death for each animal was not always a consistent time between animals. Anion gap values for some animals were in the normal range in the high CG-exposure group since the blood sample was collected greater than 10 min before death. For all the other groups, anion gap levels oscillated throughout the observation period. Both hemoglobin (Figure 3n) and hematocrit (Figure 3o) levels declined in all groups initially but returned to baseline by 8 hr. Increased variability was observed after 36 hr in surviving animals.

Tables 4a and 4b present descriptive statistics for physiologic parameters, while Figures 4a through 4i present this information graphically. As shown in Figure 4a, expired carbon dioxide levels peaked at 4 hr and decreased over time in all study groups. Inspired oxygen levels (Figure 4b) were stable throughout the study period for all groups, except for a peak in the low-CG exposure animals at 4 hr. Oxygen saturation levels (Figure 4c), measured by a respiratory gas unit on lip capillaries, generally fluctuated about the normal range in all groups (>90 %) during the study period. Steady decreases in heart rate (Figure 4d) and pulse rate (Figure 4e) were seen in control animals. For survivors of other groups, heart rate and pulse rate increased during the first 12 hr and then generally declined over the remainder of the 72-hr period. Systolic blood pressure, diastolic pressure, and mean blood pressure fluctuated in all groups during the study period, as depicted in Figures 4g, 4h and 4i.

Summary statistics for wet-to-dry lung weight ratios are presented in Table 5. Mean wet-to-dry lung weight ratios in CG-exposed animals that survived 72 hr (6.3) were similar to that of control animals (6.5), indicating that PE had resolved. Mean wet-to-dry lung weight ratios in CG-exposed animals that died (8.4) were greater than that of the control animals and CG-exposed animals that survived. The portion of the lung sampled did not appear to have any effect on lung wet-to-dry weight ratios. Impedance cardiograph readings were plotted against time for animals that survived the 72-hr study period (Figure 5a) and for animals that died on

study (Figure 5b). Linear regression models were fitted to the impedance cardiograph readings for each animal, except for animal 98-51-3 whose readings displayed excessive curvature. Impedance cardiograph readings in surviving animals showed a linearly decreasing relationship with time. Animals that died before the 72-hr study period had very few observations and hence no inference could be drawn on data from those animals.

4.0 CONCLUSIONS

4.1 Procedures Established

Table 3 presents the routine procedures and compounds used to establish the model for use in Phase II. Clinical chemistry and selected physiological endpoints remained in the normal range or were consistent with an anesthetized animal. Mild trends were noted for some parameters, but these were not clinically significant. CG exposures in the 72-hr anesthetized, ventilated swine model determined the exposure (450 mg/m^3 for 10 min) to be used in Phase II efficacy studies.

4.2 Oleic Acid Exposure

Prior to CG exposures, one animal was exposed to 3 mL of oleic acid administered i.v. over 1.5 hr. The animal died within an hour after infusion, presumably from cardiopulmonary toxic shock resulting from PE.

4.3 Phosgene Exposures

Phosgene exposures began June 22, 1998. Exposures of 10,000, 5,500, 5,000 (3 animals at this exposure), 4,500, 4,250 (2 animals), 3,750 (2 animals), 3,250, and 2,500 $mg \cdot min/m^3$ were conducted. Following the 2,500 and 3,250 $mg \cdot min/m^3$ CG exposures, animals survived for 72 hr but had PE. For both 4,250 and 3,750 $mg \cdot min/m^3$ CG exposures, one of the two animals exposed at each level survived for 72 hr and the other died within 24 hr. All had PE. At the 10,000, 5,500, 5,000 and 4,500 $mg \cdot min/m^3$ CG exposures, animals died between 10 min and 24 hr. At 5,000 $mg \cdot min/m^3$ CG, one animal died within 7 hr. Another animal given a 5,000 $mg \cdot min/m^3$ CG exposure was treated with ibuprofen at 300 mg/kg and died within 5 hr.

Table 3. Routine Procedures and Compounds Used in the Model

Procedure	Compound/Size	Dosage(Route)	Comments
Preanesthetic	Telazol®/Xylazine	0.04 mL/kg (i.m.)	5 mL of 100 mg/mL xylazine is used to reconstitute 250 mg tiletamine plus 250 mg zolazepam (Telazol). Ten min after administration, the animal was moved to surgery.
Anesthetic	Isoflurane	1.5-3 percent (Inhalation)	Administered for catheter implantation only. Animal was then weaned to a pentobarbital drip.
	Pentobarbital sodium drip	3 mL/hr of 65 mg/mL (i.v.)	Slow infusion administered to effect by an IVAC Volumetric Pump.
Muscle Relaxant	Norcuron® Vercuronium Chloride	2 mL initially (i.v.) of 1 mg/mL concentration 1 mL hourly thereafter (i.v.)	Additional 1 mL i.v. dose administered if needed.
Antibiotic	Naxcel®	1 mL of 50 mg/mL (i.m.)	Administered daily.
Endotracheal Intubation	Size 6 Fr	NA	NA
Femoral Catheters	Dual Size 7-8 Fr Size 7-8 Fr	Femoral vein Femoral artery	Dual catheter is placed in the vein to administer both the pentobarbital sodium and the Lactated Ringers solution.
Fluid Therapy	Lactated Ringer's solution	45 mL/hr	Intravenous administration.
Prepubic Urinary Catheter Placement	10 Fr Foley catheter	NA	Approximately 6 hr after start of fluid administration, a urinary catheter is inserted into the bladder using a trocar.
Aspiration	10-12 Fr pediatric catheter	NA	Hourly suctioning. 0.5 to 1 mL sterile saline placed in endotracheal tube.
Animal Rotation	NA	NA	Animal rotated every 2 hr.

An animal exposed to 4,500 mg·min/m^3 was treated with 10-15 cm water PEEP with 45 percent oxygen and survived for 14 hr. A summary statistical report found in Attachment E describes the CG dose selection for Phase II. A 10-min exposure to a target CG concentration of 450 mg/m^3 (4,500 mg·min/m^3) was selected for Phase II exposures and was determined to be an 85 percent lethal concentration in ~ 19 kg swine.

Analyses of clinical chemistry and selected physiologic parameters for the high-CG group identified the following as primary endpoints for evaluating CG exposures: P_aO_2, P_aCO_2, K, BUN, Glu, pH, SO_2, HR, and BP. Animals that survived for 72 hr returned to baseline normal ranges or to a slightly elevated normal limit. Control animals remained within the normal ranges of each parameter. Elevations were only slight and of no clinical significance. The BUN and K elevations were related to urine retention. Potassium increased to lethal levels (9 mmol/L) even though the urinary bladder was catheterized. Potassium may be an indicator of cellular damage from CG-induced PE. This model is useful in evaluating treatment regimens for respiratory casualty care individuals.

5.0 REFERENCES

See Section 5.0 of the Phase II Final Report

TASK 97-48 PHASE II

POSITIVE END EXPIRATORY PRESSURE (PEEP), IBUPROFEN (IBU), AND N-ACETYLCYSTEINE (NAC) EFFICACY STUDY IN SWINE EXPOSED TO PHOSGENE

1.0 INTRODUCTION

The earliest clinical indication of PE induced by CG is the patient's own dyspnea. Subsequently, changes in Alveolar-arterial (A-a) O_2 gradient, pulmonary auscultation, and chest radiographs are seen, in that order.[1] Aggressive supportive care must be provided to compensate for the severe dysfunction of the respiratory system associated with a phosgene (CG) inhalation exposure. Supportive therapy may include tracheal intubation and mechanical ventilation. The use of positive end expiratory pressure (PEEP) may improve oxygenation after acute exposure to toxic doses, and PEEP may need to be used to minimize pulmonary oxygen toxicity if the Fractional Inspired Oxygen (FiO_2) required to produce an acceptable level of oxygenation exceeds 0.6.[17,18] One goal is to determine a level of PEEP that produces oxygenation within normal limits combined with an acceptable FiO_2. Rodent studies reported by Dr. Alfred M Sciuto, *et al*, (1997) indicated that ibuprofen (IBU) and N-acetylcysteine (NAC) were effective treatments for CG intoxication.[26, 33] IBU and NAC have been efficacious in several acute lung injury models.[26-34]

1.1 Objectives

The main objectives of Phase II of Task 97-48 entitled "Respiratory Casualty Care Management in the Field Medical Environment" were: 1) to evaluate the impedance cardiograph (IMP) in a test system for early diagnosis of PE induced by a respiratory hazard, such as the chemical warfare (CW) gas, CG; and 2) to evaluate positive end expiratory pressure (PEEP) ventilation with high oxygen (45 percent) therapy in CG casualties. Two additional treatments, IBU and NAC, were added for evaluation shortly after Phase II had begun.

2.0 MATERIALS AND METHODS

2.1 Experimental Design and General Procedures

The test model developed and evaluated in Phase I was used in Phase II efficacy studies with seven groups of animals. Group I consisted of ventilated, anesthetized swine exposed to room air for 10 min and then administered 30 percent O_2 under physiological PEEP (3-5 cm water). Group II was exposed to approximately (~) 450 mg CG/m^3 for 10 min (4,500 mg·min/m^3 CG and given approximately 30 percent O_2 under physiological PEEP. Group III was exposed to ~4,500 mg·min/m^3 CG, and then ventilated with approximately 10-15 cm water PEEP and administered 45 percent O_2. Group IV was exposed to air for 10 min, and then administered 30 percent O_2 under physiological PEEP
and treated 30 min after exposure with a slow i.v. (over 30 min) loading dose of 45 mg IBU/kg followed by 22.5 mg IBU/kg slow infusion every 2 hr for 24 hr. Group V was exposed to ~4,500 mg·min/m^3 CG, and then treated the same as Group IV. Group VI was exposed to air for 10 min, and then given approximately 30 percent O_2 under physiological PEEP and treated with 2 mL of 20 percent NAC beginning 30 min after exposure and every 4 hr through 16 hr after exposure. Group VII was exposed to 4,500 mg·min/m^3 CG, and then given approximately 30 percent O_2 under physiological PEEP and treated the same as Group VI. The equipment, procedures, monitoring, and compounds used in this phase were the same as those used in Phase I. Lateral radiographs were taken prior to exposure, 4 hr after the end of the exposure, and then every 4 hr for 24 hr, every 12 hr for the second 24 hr, and then at termination of the experiment or death of the animal.

2.2. Test System

Fifty-four, castrated male Yorkshire purebred and crossbred swine weighing approximately 20 kg (range of 15-23 kg) when placed on study, were used in Phase II. Ten of these animals were used to select the IBU dosage and treatment regimen to be tested, and 12 animals were replacement animals. Reasons for replacing animals were respiratory congestion/pneumonia (4 animals), urinary bladder infection and ulcers (4 animals), overinflation

of the lungs (1 animal), abdominal gaseous distention with hyperkalemia (2 animals), and 1 animal with erroneous treatments due to malfunction of the infusion pump. The necropsy findings in the replaced animals were not believed to be associated with a treatment. Thirty-two animals were used in efficacy evaluation studies. Table E.3. in Attachment E lists each animal used in Phase II.

A Latin Square design was used to evaluate the three initial treatment groups of PEEP with 45 percent O_2, an air control, and a CG with no treatment exposure group. This design was modified after 2 animals to add the 4 additional exposure groups. The design was modified again, approximately two-thirds through the study, when the study director consulted with the COR and TPOC concerning the IBU treatment dosage and regimen. The 11 animals added to test the new IBU treatment regimen were equally dispersed among the remaining treatment groups, with an air and a CG exposure occurring daily.

2.3 Exposures

Animals were exposed by inhalation to either air for 10 min, or to a targeted 450 mg CG/m^3 for 10-min (4,500 mg·min/m^3). Table 1 presents the allocation of the 32 swine to the seven groups in the studies. Exposures of two animals per day were initiated on January 12, 1999. An air control and a CG-exposed animal were challenged on Mondays or Tuesdays and maintained for 72 hr or until death. Table E.4. in Attachment E is a summary of exposures, treatments, and survival times for the Phase II efficacy study.

Table 1. Animal Allocation to Treatment Groups, Number Surviving 72 hr, and Average Survival Time

Group Numbers	Exposure/ Treatment Group	Animal	Survived/N	Average Survival Time (Hr)
I	Air/None	98-110-2, 98-236-6, 99-21-1, 99-251-6, 99-287-1, and 99-288-4	6/6	72
II	CG/None	98-213-1, 98-232-2, 99-21-2, 99-255-3, 99-287-2, and 99-92-6	1/6	24.9
III	CG/PEEP	98-116-2, 98-247-1, 99-256-4, and 99-259-2	1/4	24.2
IV	Air/IBU	99-136-1, 99-146-3, 99-150-3, 99-272-2, and 99-293-2	3/5	50.5
V	CG/IBU	99-111-4, 99-136-6, 99-153-3, 99-272-3, 99-272-4, and 99-294-3	2/6	33.1
VI	Air/NAC	98-241-1 and 99-253-1	2/2	72
VII	CG/NAC	98-241-6, 98-249-1, and 99-249-5	1/3	29.6

2.4 Treatments

Physiological PEEP (3-5 cm of water) with 30 percent O_2 was administered to all animals, except those in treatment group III, as recommended by Shoemaker.[17] The PEEP in treatment group III was increased in 2-3 cm water increments at half hr intervals until 10-15 cm water PEEP was achieved. The oxygen concentrator maintained inspired oxygen at 45 percent for those animals in treatment group III.

IBU was prepared in lactated Ringer's solution for i.v. administration. The first six IBU-treated animals (2 air exposed and 4 CG-exposed) were given a slow i.v. infusion (over 30 min) loading dose of 100 mg IBU/kg at 30 min after the end of exposure, and then a slow 50 mg/kg. infusion every 4 hr through the 16th hr. The two-air exposed plus IBU treated animals survived 72 hr. One of the four CG-exposed plus IBU treated animals survived for 72 hr, and the other three animals survived less than 8 hr. The Study Director in consultation with the COR and TPOC decided that the IBU dosing interval was too long and that the dosage needed to be changed.

A loading dose of 100 mg IBU/kg followed by a continuous infusion of 100 mg/mL at a rate of 1-1.5 mL/hr was administered to two animals beginning 30 min after exposure (one exposed to air and the other to CG). Both animals died within 6.5 hr. The treatment was changed to 65 mg IBU/kg loading dose followed by a continuous infusion of 100 mg IBU/mL at a rate of 0.15-1.5 mL/hr, the air-exposed animal survived for 16 hr and the CG-exposed animal died at 4.25 hr. Further discussions were held and it was concluded that the total IBU dose should not exceed 250 mg/kg for the 72-hr study period. The treatment regimen was altered to a 30 min slow infusion of a 45 mg IBU/kg loading dose starting 30 min after the end of exposure followed by 22.5 mg IBU/kg every 2 hr through 24 hr beginning 2 hr after the end of exposure.

Limited pharmacokinetics data were collected on the IBU treated animals. A total of eleven pigs (5 in the air control group and 6 in the phosgene group) were treated with IBU in multiple-dosing experiments. Intravenous dosing with IBU was conducted during half-hour infusion periods and was repeated every 2 hr. The first (loading) dose was 45 mg/kg and the following (maintenance) doses were 22.5 mg/kg. IBU measurements were taken at approximately half-hour intervals for most animals for 26 hr. Attachment F contains the IBU Pharmacokinetics report. Attachment G contains the chemistry method for analysis of plasma IBU and the IBU dose preparation and analysis summary report.

A 20 percent commercial preparation of Mucosil (200 mg N-acetylcysteine/mL, Dey Laboratories, Napa, CA) was administered through a sterile aspiration tube placed in the trachea to approximately 2-3 cm beyond the end of the endotracheal tube. A 1-mL volume of NAC was injected through the aspiration tube, and 2 forced inspirations (block expiration for 2 cycles) using an ambu bag were administered before placing the animal back on the ventilator. The animal was turned 10 min later and a one mL volume of NAC administered again. NAC was administered 30 min after the end of exposure and then every 4 hr from the end of exposure through the 16th hr.

2.5 Statistics

2.5.1 Phase II Physiological Data

The statistics report for Phase II is presented in Attachment H and includes descriptions, definitions, analysis designations, statistical methods, data sets, and results of analysis of

physiological data. A discriminant analysis procedure was used to select respiratory, clinical chemistry, and hematology parameters that explained the greatest variability between exposure and treatment groups and were considered physiologically plausible. The primary variables considered in the discriminant analysis were summary statistics derived from the measured parameters after exploratory analyses. These are listed in Table 2 below. For parameters where a clear peak or trend was evident in visual examination of individual animal or group mean time cosurse plots, summary statistics were defined to capture that information (e.g., peak BUN, time to peak BUN, slope of chloride versus time). For other parameters, the average of readings obtained in the first 24 hr and overall averages were calculated. Additional variables considered were time to death (survival time), an indicator of whether the animal survived or died, the last timecourse during which blood chemistry and hematology parameters were recorded, and the last timecourse during which respiratory gas parameters were recorded. The SAS STEPDISC procedure was used to select variables in a stepwise approach to the discriminant analysis wherein the variable that had the greatest discriminating power at each stage was added to the model and subsequent variables were evaluated given the variables already selected. The resulting set of variables selected was assessed to determine whether any could be removed. Several exploratory models which included subsets of the data were fitted. The final model included all groups.

For each variable selected by the discriminant analysis procedure, along with a small number of variables selected by the study director, an analysis of variance (ANOVA) model was fitted to determine whether significant differences between groups were present. Pairwise comparisons among groups were made using the Tukey-Kramer method, a multiple comparisons procedure that controls the experimentwise error rate. The SAS MIXED procedure was used for these comparisons.

A repeated measures analysis of variance (ANOVA) model was fitted to the recorded values for each selected parameter during the early study period (through 8 hr). This model was used to detect early indicators of treatment effects. The model would not accept incomplete data sets (e.g., death of animals before 8 hr and missing data at early time points). The reasons for data exclusion from analysis and the animal identity associated with the exclusion are as follows: incomplete data for the analysis of respiratory parameters included animals 99-111-4 and 99-

294-3 in the CG/IBU group, animal 99-249-5 in the CG/NAC group, and animals 99-259-2 and 99-256-4 in the CG/PEEP group. Incomplete data for the analysis of blood chemistry and hematology parameters included animals 99-136-6 in the CG/IBU group and 99-249-5 in the CG/NAC group. The 8-hr reading for respiratory parameters was unavailable for some animals. In these cases, the 9-hr reading was substituted to avoid missing observations in the repeated measures analysis.

The 1-hr and 2-hr timecourse designations for the analysis of clinical chemistry and hematology parameters were combined. The repeated measures ANOVA model was fitted separately for each selected parameter and included as factors treatment/exposure group, study timecourse, and their interaction. Within animal variability was modeled as a random effect. The repeated measures models were fitted using the SAS MIXED procedure.

Linear regression models were fitted to the IMP cardiograph readings over time for each animal using the SAS REG procedure. An ANOVA model was fitted to the estimated slopes to determine whether impedance was affected by the treatment regimens. The ANOVA model included as factors the exposure/treatment group, an indicator of whether the animal survived or died, and their interaction. The ANOVA model was fitted using the SAS MIXED procedure. In addition, an F-test was used to compare the estimated slope variances between animals that died and those that survived 72 hr.

Fisher exact tests were used to compare survival rates between groups. In addition, log rank tests were used to compare the probability of survival over time between groups. A single factor ANOVA model was fitted to the lung wet to dry weight ratios (W/D R) using the SAS (V8) MIXED procedure, with exposure/treatment group as the explanatory factor. Pair-wise comparisons among groups were made using the Tukey-Kramer method. Lung W/D R were determined for the total lung by summing the weights for all lung sections of each animal, and then subtracting the total lung dry weight (D) from the total lung wet weight (W) and dividing by the total lung dry weight [(W-D)/D = W/D R].

Table 2. Variables Considered In The Discriminant Analysis

Parameter	Summary Statistics
Clinical Chemistry and Hematology Parameters	
Sodium (Na)	Overall average and average over first 24 hr
Potassium(K)	Peak potassium before 48 hr and time to Peak
Blood Urea Nitrogen (BUN)	Peak BUN and time to Peak
Glucose (Glu)	Overall average and average over first 24 hr
Chloride (Cl)	Slope of chloride versus time*
Arterial blood pH	Minimum pH and time to minimum pH
Oxygen Saturation (SO_2)	Minimum SO_2 and time to minimum SO_2
Partial Pressure of CO_2 (P_aCO_2)	Overall average and average over first 24 hr
Partial Pressure of O_2 (P_aO_2)	
Bicarbonate Ion (HCO_3)	
Total CO_2	
Base Excess (BE)	
Anion Gap (AnGap)	
Hematocrit (hct)	
Respiratory Gas Parameters	
Expired CO_2 (E CO_2)	Overall average and average over first 24 hr
Inspired O_2 (I O_2)	
Systolic Blood Pressure (SBP)	
Diastolic Blood Pressure (DBP)	
Mean Blood Pressure (MBP)	
Respiratory Rate (RR)	
Pulse Rate (PR)	Peak, overall average, and average over first 24 hr
Heart Rate (HR)	
Oxygen Saturation (S_pO_2)	Overall average, average over first 24 hr, minimum and time to minimum
Impedance	Slope of impedance versus time greater than 4 hr*
Other Parameters	
Indicator of death	Time to death (Survival Time)
Last time during which blood chemistry and hematology parameters were recorded	Last time during which respiratory gas parameters were recorded

*The SAS REG procedure was used to estimate slopes for chloride and impedance.

2.5.2. Ibuprofen Pharmacokinetics

Attachment F presents the IBU pharmacokinetics statistical report. A one-compartment, multiple-dosing pharmacokinetics model was fitted to the IBU plasma concentration data for each animal using the SAS (V6.12) NLIN procedure. Although a few blood samples were collected during the infusion period, the majority of samples were taken either immediately before or after infusion, or during the elimination phase of the most recent infusion. Therefore, the model was simplified by formulating it as a multiple-dosing series of bolus injections. Each "injection" time was defined as 25 min after the start of each dosing period, that is, approximately 5 min prior to the first blood draw following the infusion.

A dose interval variable (i) was created to facilitate the model fitting. Animals that survived the entire 24-hour dosing period received a total of 13 doses, so for those animals the dose interval variable ranged from 1 to 13. The number of doses received by animals that died before 24 hr ranged from 4 to 6. The time after dosing (t) for each sample was calculated as the number of hours elapsed since the start of the first infusion. Thus, the pharmacokinetics model for blood concentration as a function of time t can be stated as follows.

$C_1(t)$ = concentration at time t in dose interval 1 = $2A \exp(-k(t-t_1))$,
where A is the peak concentration for the maintenance dose,
t_1 is the "injection" time for interval 1 and the constant 2 accounts for the first dose being twice as large as the remaining doses;

$C_i(t)$ = concentration at time t in dose interval i ($i \geq 2$)
= $2A \exp(-k(t-t_1)) + A \Sigma \exp(-k(t-t_i))$,
where A is the peak concentration for the maintenance dose,
the sum Σ is taken over dose intervals 2 through i, and
t_i is the "injection" time for interval i.

One animal (99-294-3) was inadvertently given a second dose that was approximately as large as the first dose, so the constant 2 was also factored into the second term of the model for that animal. Two outliers were not used in modeling: for animal 99-293-2, a very low concentration of 0.05 µg/mL immediately after the 10th dose was considered suspect since it occurred where a local peak concentration should have been found. Also, for animal 99-136-6, a high concentration of 77.7 µg/mL occurring halfway between the 3rd and 4th dose was considered

suspect. On the other hand, for animal 99-272-4, a concentration of 70.2 μg/mL occurring near the end of the first dosing interval was used in the analyses, even though it was a high outlier. The use of this value did not appear to adversely affect the overall fit of the model for this animal.

For each animal, the pharmacokinetics model estimated two parameters, A and k, which are the (maintenance-dose) peak height and elimination rate, respectively. The estimated half-life (hr) of the drug was calculated as 0.693/k.[35] The modeled-based Cmax (maximum concentration) was predicted as the peak concentration that would occur immediately after the first dose. The predicted total area under the curve (AUC), from the first dose to the end of the experiment, was calculated from the model equation using the final estimated parameters for each animal. For comparison, empirical AUCs were also calculated using the trapezoidal rule.

Steady-state concentrations appeared to be achieved by the third dosing period. Therefore, the model-based average steady-state concentration was calculated as the predicted area under the curve from the third dosing time to the end of the experiment, divided by the time elapsed (hr) between the third dose and the last observation. For comparison, the average steady-state concentration was also calculated using the trapezoidal area under the curve from the third dose to the last observation.

3.0 RESULTS

3.1 Phosgene Exposure

The CG exposure of 4,500 mg·min/m^3 by probit analysis, was estimated to be lethal to 85 percent of untreated animals.

3.2 Survival Time

IBU and NAC minimally improved survival time (~33 and 30 hr, respectively) over CG/no treatment (~25 hr). Survival time following CG/PEEP with 45 percent O_2 (~24 hr) was no different than CG/no treatment. Statistical analysis of survival data indicated that there was no difference in the proportion of surviving animals in Fisher exact test comparisons between CG/no treatment and CG-exposed animals that received IBU, NAC, or PEEP treatments

($p > 0.05$ for each comparison). Survival was significantly greater in the Air/no treatment group than the CG/no treatment ($p=0.01$), CG/IBU ($p=0.03$), and CG/PEEP ($p=0.03$) groups, but did not differ significantly from the CG/NAC group ($p=0.08$) due to the small sample size for that group. Fisher's exact test could not be used to compare survival rates between the Air/treatment and Air/NAC groups, as all animals survived in both groups. Two of five animals in the Air/IBU group died, which may indicate the IBU treatment was at or near the maximum tolerated dose. However, the Fisher's exact test comparison of survival rates between the Air/no treatment and Air/IBU groups did not indicate there was a statistically significant difference in survival between these groups ($p=0.18$). The difference in survival was not statistically significant in comparisons between the Air/IBU and CG/IBU or the Air/NAC and CG/NAC groups (low sample size for both groups).

Log rank test comparisons of survival probabilities over time were in agreement with the Fisher exact test comparisons above, with the exception that survival probabilities were significantly greater in the Air/no treatment group compared to CG/NAC. The probability of survival over time was greater in the Air/no treatment group than in the CG/no treatment ($p=0.004$), CG/IBU ($p=0.02$), CG/NAC ($p=0.03$) and CG/PEEP ($p=0.01$) groups. There was no difference in survival probabilities between CG/no treatment and CG-exposed animals that received the IBU, NAC, or PEEP treatments, Air/IBU and CG/IBU, Air/NAC and CG/NAC, Air/no treatment and Air/NAC, or Air/no treatment and Air/IBU groups ($p>0.05$ for all comparisons).

3.3 Stepwise Discriminant Analysis

Six key variables were identified as explanatory variables in the stepwise discriminant analysis. These were: average P_aO_2 during first 24 hr, peak potassium level, peak BUN within first 48 hr, slope of chloride versus time, overall average pulse rate, and average inspired oxygen during the first 24 hr. Average expired CO_2 during the first 24 hr was included in the analysis, as it was identified in exploratory models but not in the final model. In addition, the study director requested analysis of the overall average Glu, Na during the first 24 hr, and the average P_aCO_2 during the first 24 hr. Box plots for these variables are displayed in Figures B-1 through B-10, of Appendix B of the Phase II Statistical Report in Attachment H. In addition, timecourse plots of

group mean scores with associated standard error bars are displayed in Figures C-1 through C-10 of Appendix C of the Phase II Statistical Report in Attachment H. Overall, the statistical analysis of the variables selected in the discriminent analysis did not indicate that the three treatments were effective. However, significant group effects were found in the ANOVA models fitted to the following parameters: average P_aO_2 during the first 24 hr ($P < 0.0001$), peak potassium level ($p = 0.0027$), peak BUN within the first 48 hr ($p = 0.0025$), expired CO_2 during the first 24 hr ($p = 0.0494$), average P_aCO_2 during the first 24 hr ($p = 0.0186$), and average inspired oxygen during the first 24 hr ($p < 0.0001$).

3.3.a Blood Gases and Physiological Measurements

Tables A2a and A2b of Appendix A in the Phase II Statistical Report in Attachment H present the summary statistics for respiratory and physiological parameters. Standard errors for HR, PR, and systolic blood pressure were high, indicating large animal-to-animal variability. Also, systolic blood pressure readings in the CG/IBU group appeared to be greater than those of other groups. HR data reflects PR data except when leads were poorly positioned during the animals side to side rotation. PR data represents the HR data since PR data are more consistent over the observation period.

- The mean P_aO_2 during the first 24 hr (Figure B-2 in Appendix B of the Phase II Statistical Report in Attachment H) in the CG/PEEP group was not different from that in the air-exposed groups, which may indicate some efficacy of the O_2 treatment. Mean P_aO_2 during the first 24 hr was depressed in the CG/no treatment, CG/NAC and CG/IBU groups relative to the air-exposed groups ($p<0.01$ for each comparison). The means were not significantly different from each other in the CG/no treatment, CG/NAC, and CG/IBU groups.

- The mean P_aCO_2 during the first 24 hr was significantly greater in the CG/IBU group when compared to the Air/IBU ($p=0.045$) and Air/no treatment ($p=0.039$) groups. Mean P_aCO_2 was increased to lower levels in the other CG-exposed groups (Figure B-10 in Appendix B of the Phase II Statistical Report in Attachment H).

- A significant group effect was detected for expired CO_2 during the first 24 hr. However, none of the pairwise comparisons indicated significant differences between groups when adjusted for multiple comparisons. The CG/IBU mean was marginally greater than the AIR/IBU mean (p=0.069) while lesser differences between the other group means were observed (Figure B-9 in Appendix B of the Phase II Statistical Report in Attachment H).

- No significant differences in the overall average pulse rate were observed among the groups, although the CG/no treatment and CG/IBU mean scores were marginally greater than all other group mean scores (Figure B-5 in Appendix B of the Phase II Statistical Report in Attachment H).

- The mean inspired O_2 during the first 24 hr was greater in the CG/PEEP group compared to all other groups, while the other groups were not significantly different from each other (Figure B-1 in Appendix B of the Phase II Statistical Report in Attachment H). This result was expected as the PEEP treatment included increased oxygen (45 percent) support, while oxygen support was maintained at a constant level (30 percent) for the other treatments.

3.3.b Clinical Chemistries

Summary tables for clinical chemistry and hematology parameters, displaying the number of observations (N), mean, and standard error for each timecourse period and exposure/treatment group, are presented in Tables A1a., A1b., and A1c. in Appendix A of the Phase II Statistical Report in Attachment H.

- On average, peak potassium levels (Figure B-3 in Appendix B of the Phase II Statistical Report in Attachment H) in the Air/IBU (p=0.009) and CG/PEEP (p=0.007) groups were significantly greater than those in the Air/no treatment control group. These levels were also increased in the CG/no treatment group compared to the Air/no treatment group, but the increase was only marginally significant (p=0.100).

No significant differences among the group means were observed for the slope of chloride vs. time, but variability appears to have increased in the CG-exposed groups, as illustrated in Figure B-4 in Appendix B of the Phase II Statistical Report in Attachment H. In addition, average slopes in the CG/PEEP, CG/IBU, and CG/NAC groups appear to be somewhat greater on average than those of air-exposed control animals and CG-exposed animals that received no treatment, although these differences were not statistically significant. Mean Cl levels steadily increased about the upper normal range over the observation period in all groups, except Group III, CG/PEEP. Group III, CG/PEEP, was the only group that returned to baseline levels.

- Standard errors for BUN and Glu were high, indicating that animal-to-animal variability was large. In the CG/IBU and Air/IBU groups, there was some evidence that glucose levels declined when BUN levels were elevated above the normal range during the first 24 hr on study.

- The mean peak BUN within the first 48 hr (Figure B-6 in Appendix B of the Phase II Statistical Report in Attachment H) of the Air/IBU group was significantly greater than that in all other groups ($p<0.05$ for each comparison), except the Air/NAC group, where variability was greater. Also, the mean BUN in the CG/no treatment group was similar to that in the Air/no treatment group, indicating that CG exposure had no effect on this variable.

- No significant differences in the overall average Glu levels (Figure B-7 in Appendix B of the Phase II Statistical Report in Attachment H) or average Na levels (Figure B-8 in Appendix B of the Phase II Statistical Report in Attachment H) during the first 24 hr were observed among the groups. Sodium levels in all study groups were within the normal range.

3.4 Early Indicators of Treatment Effect

The repeated measures analysis was used to detect early indicators of treatment effect. The timecourse variable was statistically significant at $p<0.0001$ for K, BUN, P_aO_2, PR, and expired CO_2, and at $p=0.02$ for P_aCO_2 which suggests that these variables may be early indicators of CG exposure. The effect of exposure/treatment group was statistically significant for K ($p=0.011$) and P_aO_2 ($p<0.0001$), although these differences were not necessarily indicative of treatment efficacy. As illustrated in Figure C-3 in Appendix C of the Phase II Statistical Report in Attachment H, K levels in the Air/IBU and CG/PEEP groups became elevated in the first 8 hr, while the K levels for other treatments remained within the normal range. For P_aO_2 (Figure C-2 in Appendix C of the Phase II Statistical Report in Attachment H), average levels for CG-exposed groups were lower than those in air-exposed groups, but the IBU and NAC treatments did not appear to moderate this effect. The interaction between exposure/treatment group and study timecourse was statistically significant for K, P_aO_2, PR, and expired CO_2 at $p<0.001$, for P_aCO_2 at $p=0.002$, and for BUN at $p=0.004$, which indicates that the average value of the response varied inconsistently among the treatments over the early timepoints evaluated for these parameters. The group mean plots in Appendix C of the Phase II Statistical Report in Attachment H illustrate these effects.

In general, K was observed to increase numerically by 4 hr with the peak value observed between 8-12 hr after exposure in CG-exposed animals that survived. In CG-exposed animals that died, the time course was similar. BUN in CG-exposed animals was observed to increase numerically by 8 hr and returned to around baseline levels after 16 hr in animals that survived the observation period. P_aCO_2 , PR, and expired CO_2 levels in CG-exposed animals that survived were observed to increase about 6-8 hr after exposure and fluctuated (P_aCO_2 and expired CO_2)or returned to baseline levels (PR) after 48 hr (32 hr for P_aCO_2). P_aO_2 in CG-exposed animals was observed to decrease in 1 hr after exposure. P_aO_2 was not increased above 90 mm Hg until about 36 hr for survivor animals in CG/NAC and CG/no treatment groups. P_aO_2 remained elevated >90 mm Hg in the CG/PEEP group during the observation time course until death when the P_aO_2 showed a dramatic reduction (about 65 mm Hg). P_aO_2 in survivors of the CG/IBU group did not increase above 72 mm Hg (observed at 36 hr) for the 72 hr observation period. P_aO_2 appears to be the best and earliest parameter to measure for CG-exposure.

The inspired O_2 (Figure C-1 in Appendix C of the Phase II Statistical Report in Attachment H) was a controlled parameter in the study, and was reported as significant for the group, time, and interaction between the CG/PEEP group and remaining groups. The statistical significance reported was expected. It is interesting to note that when CG/PEEP was removed from the model, the interaction effect remained significant ($p<0.0001$), largely due to the rapid decline in IO_2 observed in the Air/NAC group and the rapid increase in the CG/NAC group during the early study period. This may be related to the small number of animals tested in these groups and the sensitive regulator of the oxygen flow meter on the oxygen concentrator that required more frequent adjustments to maintain oxygen at about 30 percent.

3.4.a Blood Gases and Physiological Measurements

- For P_aO_2 (Figure C-2 in Appendix C of the Phase II Statistical Report in Attachment H), the CG/PEEP mean levels (about 100 mm Hg) remained near those of the air-exposed groups (about 97 mm Hg), while P_aO_2 levels decreased in the other CG-exposed groups (about 50 mm Hg by 24 hr, $p< 0.01$ for each CG-exposed group compared to air-exposed groups) in the early study period.

- Mean P_aCO_2 (Figure C-10 in Appendix C of the Phase II Statistical Report in Attachment H) levels rose in the CG-exposed groups (between 37 and 53 mm Hg) and declined numerically from about 38 mm Hg to about 32 mm Hg in the air-exposed groups (the decrease is not clinically significant) during the first 8 hr. After 8 hr, P_aCO_2 in CG-exposed groups tended to fluctuate at primarily upper normal levels (<38 mm Hg) except in the CG/NAC group where P_aCO_2 declined after 18 hr and remained in the lower normal range (<37 mm Hg, small n). The air-exposed groups remained about normal (35 to 45 mm Hg) with a slight decline over the course of the study.

- Expired CO_2 (Figure C-9 in Appendix C of the Phase II Statistical Report in Attachment H) levels began to rise immediately in the CG-exposed groups, while remaining stable or rising more slowly in the air-exposed groups.

- The pulse rate (Figure C-5 in Appendix C of the Phase II Statistical Report in Attachment H), in the CG-exposed groups (>142 beats per min by 6 hr post-exposure) began to rise after approximately 4 hr, while remaining stable in the air-exposed groups (generally between 80 and 120 beats per min).

3.4.b Clinical Chemistries

- For K (Figure C-3 in Appendix C of the Phase II Statistical Report in Attachment H), the Air/IBU levels were greatly elevated (a peak about 6.5 mmol/L at 12 hr) in the early study period compared to the Air/no treatment and Air/NAC groups (>4.2 mmol/L at 12 hr). In addition, the K levels in the CG/PEEP group (peak of 7.1 mmol/L at 8 hr) were elevated compared to the CG/no treatment and CG/NAC groups (<4.7 mmol/L at 8 hr), although K levels in the CG/no treatment group rose to similar levels (about 5.8 mmol/L) by 12 hr.

- For BUN (Figure C-6 in Appendix C of the Phase II Statistical Report in Attachment H), levels initially rose in all groups, but rose more rapidly in some groups (CG/PEEP, CG/IBU and Air/IBU within 8 hr).

- No findings were noted for chloride (Figure C-4 in Appendix C of Phase II Statistical Report in Attachment H), glucose (Figure C-7), or sodium (Figure C-8).

3.5 Total Lung Wet to Dry Weights

Table 3 presents the model-estimated means and standard errors of W/D R for each exposure/treatment group. The overall group effect was not statistically significant (p=0.093), although in pair-wise comparisons among groups, the CG/IBU group had a greater W/D R than the Air/IBU group (p=0.035). Table E.5. in Attachment E represents the lung wet and dry weights, and wet to dry weight ratios for each animal in each treatment.

Table 3. Phase II Model Estimates for Means and Standard Errors of Lung Wet to Dry Weight Ratios (W/D R) for Each Treatment Group

Exposure/ Treatment Group	Mean W/D R	Standard Error
Air/None	5.8	0.26
Air/IBU	5.2	0.29
Air/NAC	5.8	0.45
CG/None	5.6	0.26
CG/IBU	6.5	0.26
CG/NAC	5.9	0.37
CG/PEEP	5.7	0.32

3.6 Impedance Cardiograph

The linear regression models fitted to the impedance cardiograph readings overlaid on the observed data for each animal are presented in Appendix D of the Phase II Statistical Report in Attachment H. It is evident from these plots that the impedance cardiograph readings in surviving animals generally decreased over time, except for animal 99-272-2 (Air/IBU) whose readings initially declined and then began to rise, and animal 98-232-2 (CG/None) whose readings increased over time. The impedance readings displayed no consistent trend among animals that died before 72 hr. While impedance appeared to decline at a more rapid rate for some, rapid increases were observed in others. ANOVA results indicated that mean slopes did not vary among the exposure/treatment groups, nor between animals that survived or died. The variability in slopes was significantly greater ($p<0.0001$) among animals that died.

3.7 Ibuprofen Pharmacokinetics Results

The Statistical Report for Ibuprofen Pharmacokinetics is in Appendix F. IBU therapy with repeated IBU infusions targeted a plasma concentration range of 20 to 100 μg/mL and the actual observed plasma concentrations ranged between 3 and 155 μg/mL. The observed C_{max} of the IBU loading dose in air-exposed animals ranged from 88 to 155 μg/mL with an average of 116 μg/mL, and in CG-exposed animals, the average C_{max} was 114 μg/mL. The estimated half-life ranged from 0.6 hr to 1.4 hr with a mean of 52 min in air-exposed animals and 0.5 to 0.8 hr with a mean of 38 min in CG-exposed animals. The trapezoidal average steady state plasma IBU

concentration ranged from 26 to 53 μg/mL with a mean of 35 μg/mL in air-exposed animals and 25 to 40 μg/mL with a mean of 29 μg/mL in CG-exposed animals. Steady state was achieved ~4 hr after the end of the inhalation exposure in both groups. Trapezoidal averages for area under the concentration-time curve measured over 24 hr ranged from 457 to 1010 μg mL^{-1} hr with a mean of 783 μg mL^{-1} hr in air-exposed animals and 231 to 881 μg mL^{-1} hr with a mean of 543 μg mL^{-1} hr in CG-exposed animals. Areas under the concentration-time curve and steady state values estimated from the model were comparable to, but generally less than, those observed.

3.8 Histopathology

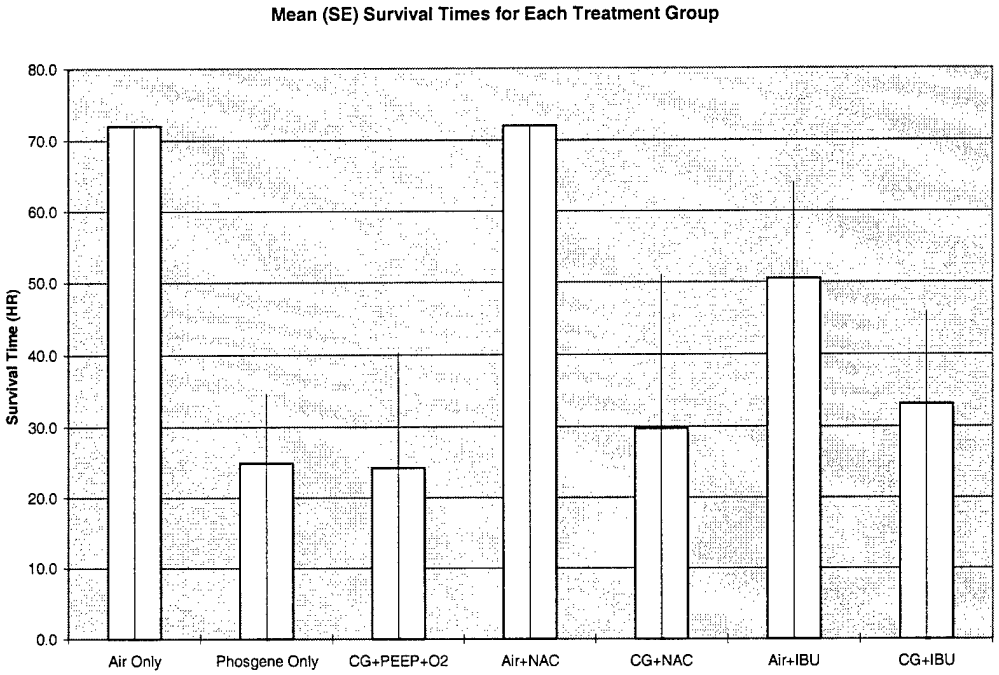
Histopathology results for Phase and II data have not been provided by USAMRICD and are not included in this report.

4.0 CONCLUSIONS AND DISCUSSION

Although limited evidence of treatment efficacy was noted, none of the treatments appeared to be consistently effective in moderating the effects of an LCt_{85} CG exposure. IBU and NAC minimally improved survival time (~33 and 30 hr, respectively) over CG/no treatment (~25 hr). Survival time following CG/PEEP with 45 percent O_2 (~24 hr) was no different than CG/no treatment. Figure 1 demonstrates this graphically.

Potassium, P_aO_2, P_aCO_2, PR, and expired CO_2 may be useful early indicators of CG exposure. In animals that died, K levels generally rose within 12 hr (as early as 4 hr) to > 6 mmol/L (> 9 mmol/L at time of death). In the air control groups, except Air/IBU, observed K levels increased slightly within 8 hr to < 6 mmol/L before returning to normal. This was most likely a result of urine retention, and the effect is the same with BUN. Air/IBU animals showed a greater increase in K levels early (within 8 hr) in the study period than CG/IBU treated and air-exposed control animals. This may be related to a reduction in excretion of K and a possible decrease in renal blood flow caused by IBU treatment. The addition of CG exposure may have resulted in over-riding renal effects (increased K excretion and renal blood flow, and decreased fluid loss with water re-absorption). These hypotheses were not tested in this study. K levels in

FIGURE 1. SURVIVAL TIMES FOR EACH TREATMENT GROUP IN PHASE II



CG-exposed animals that survived generally rose to > 6 mmol/L within 8 hr before returning to normal within 16 hr. The exception was the CG/no treatment group that increased to similar K levels in 12 hr. The difference in time to peak may be related to the time of death for the animals in that group. Groups with a high number of early deaths (< 12 hr) had increased K levels earlier than groups whose animals died at later time points (>12 hr). P_aO_2 levels in CG-exposed animals decreased over time until death, except in animals treated with PEEP and high O_2 (45 %), which had P_aO_2 levels similar to air controls until near death. P_aO_2 was the only parameter observed to change at about 1 hr in CG-exposed animals and provided the earliest indication of CG-exposure. Air-exposed groups had P_aO_2 levels within the normal range. P_aCO_2 increased over the first 8 hr in the CG/IBU group before returning to normal values after 24 hr. The remainder of the CG-exposed groups showed greater fluctuation as the P_aCO_2 increased over time. The P_aCO_2 in air control groups remained about normal. For expired CO_2, levels began to rise immediately in the CG-exposed groups, while remaining stable or rising more slowly in the air-exposed groups. Pulse rate in the CG-exposed groups began to rise after approximately 4 hr, while remaining stable in the air-exposed groups.

The lung W/D R as measured in this study was not indicative of CG-exposure or of treatment efficacy. Mean W/D R was similar in the CG/None and Air/None groups, and the mean W/D R in the CG/IBU group was significantly greater than that in the Air/IBU group. However, there were no significant differences among CG-exposed groups.

There was evidence (P_aO_2 results) to suggest that PEEP treatment with 45 percent O_2 mitigated the effect of CG on P_aO_2, presumably due to the increased oxygen support and the PEEP forcing O_2 across the alveolar-capillary membrane. Using PEEP (10-15 cm of water) and high oxygen (45 percent) supportive therapy along with a standard PE treatment regimen, but not as a stand alone treatment, may increase survival of CG respiratory casualties. Histopathology is needed to assess if lung damage occurred as a result of PEEP (10-15 cm of water).

IBU and NAC, as stand alone therapies, improved the survival time compared to the CG/no treatment group. Necropsy of CG-exposed animals treated with IBU or NAC indicated that the degree of froth within the trachea and larger bronchi was noticeably less than in the CG/no treatment group. However, the lung W/D R did not provide the expected results of CG-exposed groups being significantly greater than Air-exposed controls. Two possible

explanations exist. The first was study design. The air-exposed control animal was not sacrificed at the time of death of the CG-exposed animal, and therefore the survival time was not equivalent between the two groups. Air control animals survived the complete 72-hr observation period, whereas CG-exposed animals survived 4 to 72 hr. Development of PE and resolution could be in various stages. A second possible reason was that animals received a continuous infusion of 45 mL/hr of lactated Ringer's solution until death or study termination. This may have increased the fluid load on some animals. Most animals appeared to correct for the fluid therapy, but there was concern with the IBU-treated group. Overall urine output was monitored and appeared to be reduced in the IBU-treated groups. Timed measurements of urine output should be accomplished in future studies.

Greater variability in the slope of impedance versus time was noted among animals that died compared to those that survived, although the effect did not appear to be treatment-related. In this model, the impedance cardiograph was not an effective instrument for detecting early PE. This may be the result of anatomical differences between swine and human beings. The subcutaneous fat layer is thicker in swine, particularly in the neck and shoulders where the reference and measuring bands were attached.

The key variables identified in the discriminant analysis were: peak potassium level, peak BUN within the first 48 hr, slope of chloride concentration versus time, average inspired oxygen during the first 24 hr, expired CO_2, average P_aO_2 during the first 24 hr, average P_aCO_2, and overall average pulse rate. Of these, K, P_aO_2, P_aCO_2, pulse rate, and expired CO_2 were identified as possible early indicators (~4 hr observed changes) of CG exposure. Also identified as early indicators, but not considered relevant by the study director, were BUN and inspired O_2. The BUN increase, particularly between 4 and 18 hr, is most probably related to the retention of urine. Generally, the BUN declined within 4-8 hr after the urinary bladder was catheterized. The inspired O_2 was set by the study protocol. Except for the CG-exposed treated with PEEP and 45 percent O_2, animals were maintained at about 30 percent O_2.

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ATTACHMENT A

Protocol 132

Study performed by

Battelle Memorial Institute
Medical Research and Evaluation Facility
505 King Ave., JM-3, Columbus, Ohio 43201-2693

Study Title:

Respiratory Casualty Care Management in the Field Medical Environment

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Statistical Review:
Ronald G. Menton, Ph.D.

Contracting Officer's Representative:
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USAMRICD

MREF Chemistry Review:
Timothy L. Hayes, B.A., Study Chemist

Aerosol Physicist:

Mark R. Perry, M.S., Research Scientist

Environmental Safety and Health Review:

David L. Stitcher, C.I.H., Environment, Safety, and Health Officer

Quality Assurance Review:

7/17/97

Elisha N. Morrison, M.S., Quality Assurance Specialist

Study Director:

Frances M. Reid, D.V.M., Study Director

Protocol Title: Respiratory Casualty Care Management in the Field Medical Environment

I. Study Director: Frances M. Reid, D.V.M.

II. Co-Investigators:

A. Study Statistician: Ronald G. Menton, Ph.D.

B. Study Veterinarian: Tracy A. Peace, D.V.M., M.S.

C. Sponsor: U.S. Army Medical Research and Materiel Command (USAMRMC)

D. Sponsor Monitor: LTC Richard R. Stotts, D.V.M., Ph.D., U.S. Army Medical Research Institute of Chemical Defense (USAMRICD)

III. Non-Technical Synopsis:

The main objectives of this task are to evaluate the impedence pneumograph in a test system for assessing the efficacy of medical treatment and management of chemical warfare (CW) phosgene casualties and to evaluate positive pressure ventilation therapy. Treatment of CW casualities has not been thoroughly studied. The areas of concern with choking agents, such as phosgene, include pulmonary edema, hypoxia, hypotension, secretions, bronchospasm, right heart failure, and infection. With the development and successful application of a test system, therapies tested and information gained will enable the field clinician to more effectively diagnose, treat, and manage CW casualties.

This study is designed in two phases. Phase I is a pilot study to evaluate the feasibility of using anesthetized swine and the impedence pneumograph to evaluate therapies for pulmonary edema. Phase I includes equipment installation and demonstration of adequate performance, writing of Standard Operating Procedures (SOPs), and a determination of phosgene exposure-pulmonary response in anesthetized swine to determine a challenge to be used in Phase II. Data obtained from this study also will be used to identify endpoints and time points to be used in Phase II.

Phase II is a treatment efficacy experiment. This experiment is designed to use the test system evaluated in Phase I to determine the treatment efficacy of early administration of positive end expiratory pressure (PEEP) ventilation and respiratory assistance in animals

exposed to phosgene. There are three groups of animals in this phase. Group I consists of anesthetized swine exposed to clean air for 10 min, then mechanically ventilated, and administered 21 percent O_2. Group II consists of anesthetized swine exposed to phosgene for 10 min, ventilated, and administered 21 percent O_2. Group III consists of anesthetized swine exposed to phosgene for 10 min, and then ventilated with approximately 10-18 cm water PEEP, and administered 45 percent O_2. Animals will be monitored 24 hr a day for up to 3 days.

IV. Background:

A. Background: Choking agents, such as phosgene, irritate the tracheobronchial tree and produce pulmonary edema (Moore and Gate, 1946). Although choking agents are very effectively screened by a properly worn and maintained gas mask, substantial toxicity may occur before the individual becomes aware of an exposure and dons a mask. The earliest evidence of a toxic exposure may be tachypnea or dyspnea. This is a serious problem because, even after lethal exposures, the clinical findings of abnormal lung sounds, radiologic evidence of infiltrate, blood gas abnormalities, and other evidence of impending pulmonary edema may not appear until two to six hr after exposure. The development of new techniques for rapidly and accurately determining exposure to choking agents and better therapies to assist the battlefield clinician in the treatment of soldiers in the field are imperative.

The management of respiratory system toxicity is a formidable problem. Post-exposure chemical treatment has not been thoroughly studied. The areas of concern include pulmonary edema, hypoxia, hypotension, secretions, bronchospasm, right heart failure, and infection. The pulmonary edema observed subsequent to inhalation of choking agents has been treated by a number of techniques (Urbanetti, 1989). Reduction of pulmonary artery pressure appears to be of some value. Positive pressure ventilation decreases the speed and the severity of capillary leakage and should probably be instituted early.

Following phosgene exposure, the patient is often aware of his limited pulmonary function and impending respiratory disaster long before medical personnel are able to corroborate this by physical exam, X-ray, or arterial blood gas (ABG) measurements. Typically, after exposure, there is a latent period of four to six hours before substantial changes are evident on physical examination, ABG, or chest X-ray. The earliest clinical indication of pulmonary edema is the patient's own dyspnea. Subsequently, changes in Alveolar-arterial (A-a) O_2 gradient, pulmonary auscultation, and chest radiographs are seen, in that order (Urbanetti, 1988). Aggressive supportive care must be provided to

compensate for the severe dysfunction of the respiratory system associated with an inhalation exposure to phosgene. Supportive therapy may include tracheal intubation and mechanical ventilation. The use of PEEP may improve oxygenation after acute exposure to toxic doses, and PEEP may need to be used to minimize pulmonary oxygen toxicity if the Fractional Inspired Oxygen (FiO_2) required to produce an acceptable level of oxygenation exceeds 0.6. One goal is to assess a level of PEEP that produces oxygenation within normal limits combined with an acceptable FiO_2.

B. Literature Search:

1. Literature Source(s) Searched:

The U.S. Army Medical Research Institute of Chemical defense (USAMRICD) and Battelle conducted literature searches of the National Agriculture Library (AGRICOLA), Defense Technical Information Center (DTIC) and of the following data bases: MEDLARS II, National Library of Medicine, National Interactive Service, MEDLINE, and TOXLINE. The last two sources are routinely searched for publications relating to animal use, methodology, therapies, models, and alternative methods used for Chemical Surety Materiel (CSM) and threat agents (such as phosgene, cyanide, etc.). COMPMED was also searched.

2. Date and Number of Search: April 30 and April 17, 1997 were search dates for MEDLINE and TOXLINE. May 1997 has been the most recent search of COMPMED.

3. Key Words of Search: phosgene, pulmonary edema, positive-pressure respiration/ventilation, swine, inhalation, anesthesia, pressure breathing, positive end expiratory pressure (PEEP), oxygenation, prolonged anesthesia, humans, non-human primate, oleic acid, and various combinations thereof.

4. Results of Search: This effort does not duplicate any on-going or completed research projects.

V. Objective/Hypothesis:

This study is designed to assess the early detection of pulmonary edema using the impedence pneumograph, and to assess the early application of PEEP to treat phosgene-induced pulmonary edema in swine.

VI. Military Relevance:

A wide variety of chemical exposures, both belligerent and accidental, may occur under battlefield conditions. One of the missions of USAMRICD is to provide medical management techniques for chemical casualties. The need for knowledge of potential avenues of therapy for phosgene exposure is critical. The unique emphasis on research and products particularly relevant to clinical management is identified in the Joint Service Agreement, USA code S-A-304 and in the Medical Chemical Defense Work Breakdown Structure, WBS codes 6.6.1.4.7.7.4.

VII. Materials and Methods

A. Experimental Design and General Procedures:

General Procedures: Immediately before testing, swine will be immobilized with an appropriate sedative or tranquilizer, such as Telazol® and xylazine combination given intramuscularly. Animals will be anesthetized with an appropriate intravascular drip-type anesthetic, such as Nembutal® (pentobarbital sodium). Pentobarbital sodium is recommended for its effective analgesia and blockage of pharyngeal-laryngeal reflexes. Atropine will be given subcutaneously (SQ) to counteract excessive secretory response and to decrease peristalsis (Castleman et al.,1979). An eye ointment will be administered periodically on an as needed basis.

Following induction of anesthesia, the animal will be intubated with an appropriate size endotracheal tube. A laryngoscope may be used to facilitate the insertion of the endotracheal tube and to minimize laryngeal and tracheal trauma.

Exposure System Design and Characterization:

System Design: The proposed exposure system to be used during the vapor exposure tests is shown schematically in Figure 1. This system is designed to operate in 4 modes: Miran Calibration, Exposure Concentration Quantification, Animal Exposure, and Exhaust.

In Miran Calibration Mode, calibrated volumes of know phosgene concentration gas are introduced through a septum of a closed-loop system. A Metal Bellows® pump will circulate phosgene/air mixture through a Miran (1A or 1B)detector. The calibration system will have a known internal volume. Miran output as a function of phosgene

concentration will be plotted and used to quantify the phosgene concentration.

In the Exposure Concentration Quantification Mode, controlled flows of phosgene and zero air are mixed and directed through the Miran into the reservoir plenum and out through the exhaust system. Phosgene concentration is quantified via the Miran and gas samples are collected from the reservoir plenum via an airtight syringe. The gas samples will be analyzed using gas chromotography equipped with a flame ionization detector (GC-FID).

In Animal Exposure Mode, the two-way valve going from the reservoir plenum to the ventilator is opened, allowing exposure of the anesthetized pig to the phosgene/air. Target exposures will be for 10 minutes. Exhalation flow will be directed to the exhaust treatment system. Gas samples will be collected and analyzed during each animal exposure.

In Exhaust Mode, the entire system flow is drawn directly to the exhaust treatment system. Bubbler samples can also be collected. The exhaust treatment system removes the phosgene via a caustic bubbler and charcoal filter combination.

System Characterization: System characterization will include leak testing, flow calibrations, and internal volume measurements (calibration loop), Miran calibration, GC-FID calibration, efficacy of gas sample collection and analysis, and overall system stability. Calibration curves will be prepared for the Miran (phosgene concentration vs Miran output) and the GC-FID (phosgene concentration vs peak area count). Phosgene concentration results from the Miran and GC-FID analysis of the gas samples will be compared. The ventilator will be integrated into the system to assure proper operation.

In Phase I, up to 5 animals will be exposed and monitored to determine the time course of specified endpoints which might be employed in the Phase II efficacy study. Parameters relevent to the pilot study exposures will be documented.

In the Phase II Efficacy Study, three groups with 6 swine in each will be used to determine the efficacy of PEEP. Two of these groups will be exposed to phosgene concentrations determined from Phase I results.

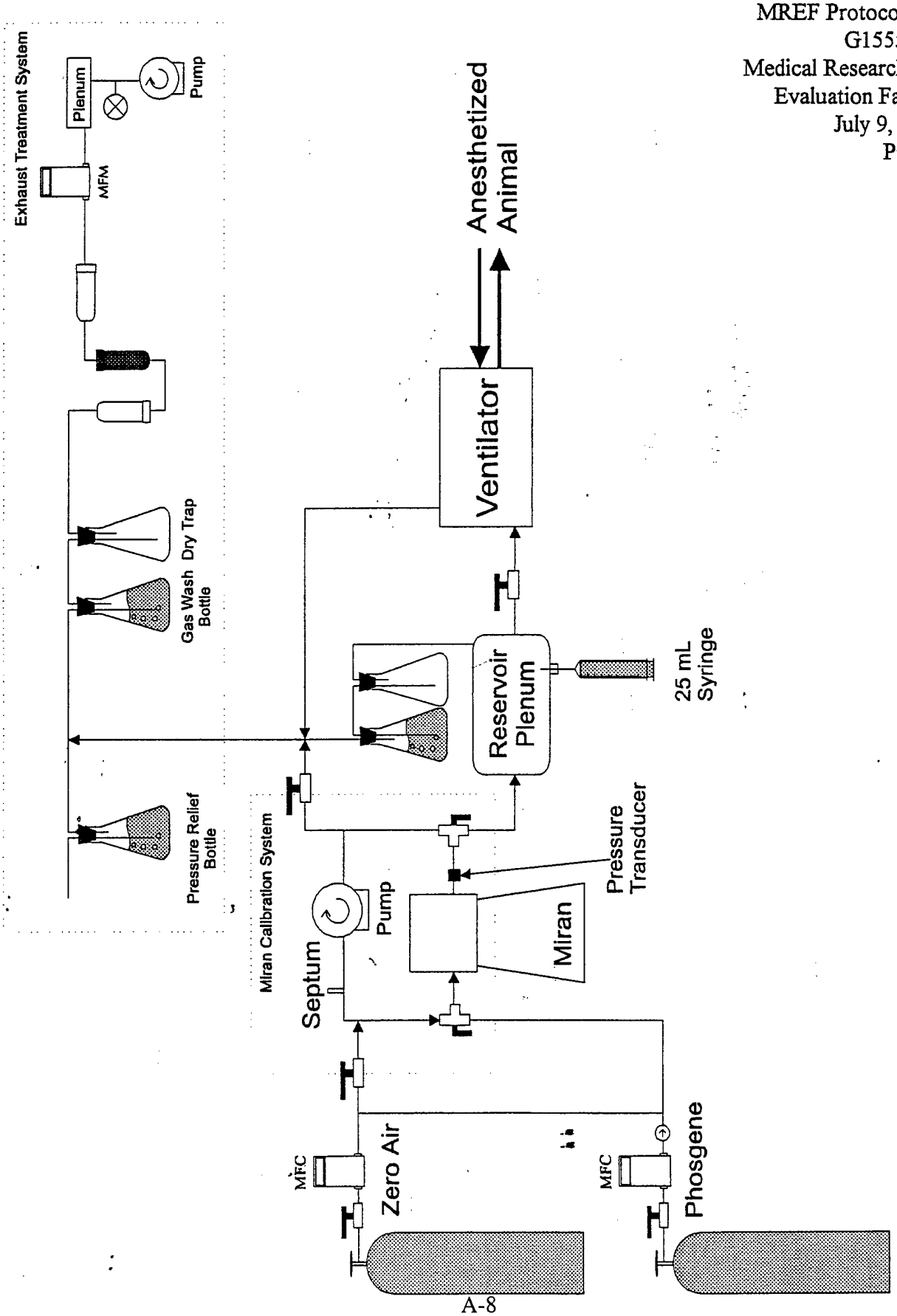

Figure 1. Schematic of Phosgene Exposure System

B. Study Design:

1. Phase I - Pilot Study

a. Up to five animals (Sus scrofa) will be used to select a phosgene exposure to be used in Phase II and to evaluate techniques to allow the pigs to be continuously anesthetized for up to three days. Animals will be anesthetized as described in section VII.D.1.b.(1). Animals will be catheterized, and exposed to concentrations of phosgene, using an initial exposure of 2000 $mg*min/m^3$. Depending upon results, an additional animal may be exposed to the same concentration or to an adjusted concentration. After each exposure, the results will be evaluated by the Study Director in consultation with the Contracting Officer's Representative (COR) and Scientific Technical Objective (STO) Coordinator. Selected endpoints to be measured include, but are not limited to, impedance pneumogram, lethality (to include time interval to death), arterial and venous blood gases, heart rate, and respiratory rate (discussed in section VII. D. 6.). Lethality at 48 hr post-exposure is a primary endpoint. Up to two animals may be anesthetized and exposed per day, and they will be monitored 24 hr per day for up to 3 days.

2. Phase II - Efficacy of Positive End Expiratory Pressure Ventilation

Three groups with 6 swine in each are used to determine the efficacy of PEEP in reducing the pulmonary edema induced by phosgene inhalation. The following groups will be used:

a. 6 swine exposed to filtered clean air;
b. 6 swine exposed to phosgene concentration as determined in Phase I
c. 6 swine exposed to phosgene concentration as determined in Phase I followed by immediate positive pressure ventilation and respiratory assistance.

Animals will be anesthetized, mechanically ventilated and exposed to either filtered clean air or a phosgene concentration selected from data from Phase I. Physiologic endpoints selected from Phase I data are monitored. Anesthetized animals may be monitored for up to 3 days if this is determined to be necessary by the Study Director in consultation with the COR and STO coordinator.

C. Laboratory Animals Required and Justification:

1. Non-animal Alternatives Considered:

Computer simulation of inhalation studies has been performed at USAMRICD; however, this approach requires data from animals to develop and validate the type of model that best fits actual signs. In addition, although *in vitro* studies have helped in understanding some of the basic biochemistry and cellular toxicity of phosgene, intact animals are needed for a more complete characterization of the pulmonary pathophysiology, clinical presentation, and natural course of phosgene intoxication. All these studies are expected to benefit mankind by allowing the early recognition of incipient pulmonary edema from phosgene and the development of more effective treatments for respiratory casualties. *In vitro* methods can not replace the *in vivo* models when evaluation of physiological responses to pulmonary edema, the healing process, and the multiplicity of physiologic interactions, as well as the animal's interaction with its environment, serve as analytical endpoints.

2. Animal Model and Species Justification: The use of nonhuman primates in environmental pollution research has been discussed by Castleman and colleagues (1979) of the California Primate Research Center. These researchers, actively involved in inhalation studies, have addressed the nature of the small airways and respiratory mechanical properties in macaques and concluded that the "structure and number of generations of respiratory bronchioles are similar between man and macaques." Swine have been used extensively in cardiovascular studies, and in accordance with the 3 "Rs" of Russell and Birch (Replacement, Refinement, and Reduction), we propose to use swine instead of monkeys. Swine approximate lung size and respiratory tidal volume of man. Rodents do not approximate the size, respiratory tidal volume, or lung compliance of man.
3. Laboratory Animals:

a. Genus & Species: Sus scrofa (Swine)

b. Strain/Stock: Cross-bred or purebred Yorkshire, Landrace, Large White, or Duroc.

c. Source/Vendor: Isler Genetics or an alternative specific pathogen free (SPF) herd or equivalent. Isler Genetics is located in the vicinity of Prospect, Ohio.

d. Age: Approximately 6-11 weeks of age upon receipt.

e. Weight: Approximately 16-20 kg (35-45 lbs) at dosing. Weight takes precedence over age.

f. Sex: Castrated male.

g. Special Considerations: Specific Pathogen Free. The respiratory and cardiovascular systems, to the best of the vendors knowledge, will be clear and free of any disease.

4. Total Number of Animals Required: 23 (does not include replacements needed).

5. Refinement, Reduction, Replacement:

a. Refinement: Animals are anesthetized as described in section VII.A. and are maintained in an anesthetized state. Animals are not allowed to recover from anesthesia.

b. Reduction: Experiments are conducted in a phased fashion to limit the number of animals used to the minimum necessary to achieve statistically valid results. Procedures are stated for stopping experimentation if problems are encountered. The Phase I Pilot Study is conducted in an up-down design to limit the number of animals.

c. Replacement: Treatment of cardiovascular effects following exposure to phosgene has not been thoroughly studied. To evaluate treatment and early diagnostic methods, a whole animal model needs to be developed.

D. Technical Methods:

1. Pain:

a. USDA (Form 18-23) Pain category:

Animals will be placed in Category D (alleviated pain). There is no pain associated with phosgene exposure, although the development of pulmonary edema can be accompanied by respiratory distress or mild pain (Diller, 1985). Animals will be anesthetized prior to, during, and following phosgene exposure and will not be allowed to recover from anesthesia at experimental completion.

(1) No Pain - (Column C): NA

(2) Alleviated Pain - (Column D): 23 (100%)

(3) Unalleviated Pain or Distress - (Column E): NA

b. Pain Alleviation:

(1) Anesthesia/Analgesia/Tranquilization:

Atropine (0.05 mg/kg) SQ will be given to counteract the excessive secretory response observed as a side effect of anesthetization and to decrease peristalsis. Initial sedation will be accomplished by administration of an appropriate sedative, tranquilizer or light anesthetic, such as tiletamine and zolazepam (Telazol®, 250 mg of each), diluted with 5 mL xylazine (100 mg/mL) and dosed at 4.4 mg/kg xylazine IM, or acetyl promazine at 0.5 mg/kg and ketamine at 15 mg/kg given IM. Pentobarbital sodium (Nembutal®) at a dosage of approximately 24 mg/kg IV may be used to establish deep anesthesia, and vecuronium bromide (Norcuron®) at a dose of 0.1 mg/kg IV may be used to provide muscle relaxation. Animals will be intubated and anesthesia will be maintained by using an IV drip of an appropriate anesthetic, such as Nembutal® at a dosage rate of approximately 10 mg/kg/hr and IV infusion of 0.010-0.015 mg/kg of Norcuron®. Nembutal® was selected for its effective analgesia and blocking of pharyngeal-laryngeal reflexes. An IV infusion of Lactated Ringers solution (approximately 45mL/hr) or other appropriate fluid therapy will be given on an as needed basis during anesthesia to maintain blood volume and pressure.

(2) Paralytics: Vecuronium bromide (Norcuron®) was selected as an adjunct to general anesthesia to facilitate endotracheal intubation and to provide skeletal muscle relaxation during mechanical ventilation (Norcuron®, Physicians Desk Reference, 47th ed, pp 1698-1700, 1993).

c. Alternatives to Painful Procedures:

(1) Source(s) Searched: Medline, Toxline, Embase, Biosis Previews, Sedbase

(2) Date of Search: June 1997

(3) Key Words of Search: Long-term (prolonged) anesthesia, pentobarbital, nembutal, alternatives, substitutes, injectables, swine

(4) Results of Search: There are no suitable alternatives to possible painful proceures which will meet study objectives.

d. Painful Procedure Justification: Biomedical experiments which may potentially cause more than momentary or slight pain or distress to animals will be relieved with the use of anesthetics. In searching for alternatives to such procedures, it has been determined that alternative procedures are not available to accomplish the objectives of the proposed experiment.

2. Prolonged Restraint: Prolonged physical restraint will not be used. Animals will be restrained chemically by general anesthesia for up to 3 days. Animals will not recover from anesthesia. Perfusion of lung tissue and necropsy will be performed at the completion of each experiment. Prolonged anesthesia is necessary for developing an intubated animal model to evaluate the pulmonary edema induced by phosgene exposure and to evaluate the efficacy of candidate therapies. Animals under anesthesia will be monitored continuously by trained individuals.

3. Surgery:

a. Procedure: Catheters will be placed in a femoral artery via a cutdown incision and will be used for collecting blood for blood gas analyses and may be used to measure blood pressure. A catheter also will be placed in the femoral vein and

used for infusion of fluids/lipids and for blood collection. Other catheters may be placed in alternative vessels for additional physiological measurements (e.g., central venous pressure, pulmonary artery pressure) or administration of therapeutic compounds (e.g., antibiotics). Incisions will be closed with metal skin clips or other appropriate closure material. Surgical implantation of catheters will be performed using aseptic techniques. Chest radiographs will be taken at times determined from the Phase I results to assess pulmonary edema.

b. Pre- and Post Operative Provisions: Animals will be examined, before use, by a staff veterinarian for general health status.

c. Location: Generally, at the MREF in Room 9 of JM-3.

d. Multiple Survival Surgery Procedures: NA

(1) Procedures: NA

(2) Scientific Justification: NA

4. Animal Manipulations:

a. Injections: Preanesthetics, anesthetics, fluid therapy, and a skeletal muscle relaxant administered as described in section VII.D.1.b.(1) are expected to be given. Other supportive injections may be given if the Study Veterinarian, Study Director, or COR, in consultation with the STO coordinator find it necessary.

b. Biosamples: Arterial and venous blood samples are collected during most phases. Other biosamples may be taken if directed by the STO coordinator and COR.

c. Animal Identification: Animals are uniquely identified by an appropriate method for the species, such as ear tag, ear notch, or tattoo.

d. Behavioral Studies: None

e. Other Procedures: Necropsy - Animals may be necropsied at the termination of each study. The STO coordinator and COR are to determine which animals

require necropsy. When necropsies are performed, lung weight will be determined followed by lung insufflation with fixative. The lung parenchyma and airways will be processed for histopathologic analysis and electron microscopy.

5. Adjuvants: NA

6. Study Endpoint: One or more of the following endpoints may be measured in this study: impedance pneumograph, lethality, arterial and venous blood gases, heart rate, and respiratory rate. Animals are maintained in deep anesthesia for up to 3 days or until death following phosgene exposure. On Day 2 (Day 0 being day of exposure), after sample collections, the animals will be euthanatized, and necropsies performed as described in VII.D. 4.e.

7. Euthanasia: Animals will be euthanatized by an approved method as described in the 1993 Report of the AVMA Panel on Euthanasia, such as by an overdose of pentobarbital sodium (100 mg/kg) IV, or 1 mL/10 lbs of Beuthanasia® IV. The remains will be disposed of by incineration in accordance with appropriate SOPs.

D. Veterinary Care:

1. Husbandry Considerations:

a. Study Room: Animals will be dosed within a chemical fume hood at the MREF. Approximately 1 hr after exposure cessation, the animal may be removed from the hood.

b. Special Husbandry Provisions:

Anesthetization, Exposure, and After Exposure: Long-term anesthesia poses special concerns. Body heat will be maintained by using a warm air-flow blanket wrapped around the animal. Prolonged recumbency can cause hypostatic congestion of dependent areas, especially lungs. To prevent the congestion, animals will be turned from side to side approximately hourly or as determined necessary. The animals may receive oxytetracycline to help prevent bacterial pneumonia. Other antibiotics may be administered based on clinical observations and the experience of staff veterinarians. Intravenous nutrients such as lipids, amino acids, etc., will be given at a minimum of twice daily during anesthesia to help meet metabolic requirements during long-term anesthesia.

Diet - Prior to study, animals are fed a commercial pig chow or producer-purchased grower or maintenance ration in accordance with Battelle SOP MREF. VII-027. If the commercial diet fed at Battelle's MREF is different than those fed by the vendor, then the diet will be converted to this new feed over a period of several days. No known contaminants that would interfere with the results of the study are known to be present in the feed. Analysis of the feed may be obtained from the commercial source or may be analyzed as deemed appropriate by the Study Director and/or the Study Veterinarian. Animals are fasted a minimum of 8 hr prior to induction of anesthesia.

Water - Water will be provided *ad libitum* except during anesthesia. Water is supplied from the Battelle water system, and is given *ad libitum* during quarantine and holding. No contaminants that would affect the results of the study are known to be present in the water.

Housing - Animals may be group or individually housed in units meeting the requirements of the Guide for the Care and Use of Laboratory Animals, or as directed by a Battelle veterinarian. Animal caging will be changed per Battelle SOP MREF. VII-027.

Lighting - Animals are maintained under fluorescent lighting with a light/dark

cycle of approximately 12 hr each per day.

Temperature - Air temperature in animal rooms will be maintained in the range of 50 to 80 degrees F in accordance with Battelle SOP MREF. IV-001. At least 90 percent of the total twice-daily measurements will fall within this range.

Relative Humidity - Relative humidity in animal rooms will be maintained in the range of 30 to 70 percent in accordance with Battelle SOP MREF IV-001. At least 90 percent of the total twice-daily measurements will fall within this range.

Quarantine - Animals will be examined for evidence of disease and placed in quarantine for fourteen days.

Replacements - An animal found unfit for study during the quarantine or acclimation periods may be replaced by another animal. If an animal is replaced, any data collected on the original animal are retained and the reason for replacement documented.

Laboratory Animal Welfare Practices - Battelle's Animal Resources Facilities have been registered with the U.S. Department of Agriculture (USDA) as a Research Facility (Number 31-R-021) since 14 August 1967 and are periodically inspected in accordance with the provisions of the Federal Animal Welfare Act. In addition, animals used in research are obtained from laboratory animal suppliers duly licensed by the USDA or reviewed and/or inspected by Battelle's Laboratory Animal Veterinarian. Battelle's statement of assurances regarding the Department of Health and Human Services (DHHS) policy on humane care of laboratory animals was accepted by the Office of Protection from Research Risks, National Institute of Health (NIH) on 27 August 1973. Animals at Battelle are cared for in accordance with the guidelines set forth in the "Guide for the Care and Use of Laboratory Animals" (1996), and/or in the regulations and standards as promulgated by the Agricultural Research Service, USDA, pursuant to the Laboratory Animal Welfare Act of 24 August 1966, as amended.

Accreditation - On 31 January 1978, Battelle's Columbus Division received full

accreditation of its animal-care program and facilities from the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC). Battelle's full accreditation status has been renewed after every inspection since the original accreditation. The MREF is a part of the facilities granted full accreditation.

Protocols - Protocols of all experiments using animals are reviewed and approved by Battelle's Institutional Animal Care and Use Committee (IACUC) prior to initiation of the study. Once Battelle's review is complete, the protocol and Battelle's IACUC review is sent for review and approval by the USAMRMC Veterinarian.

2. Attending Veterinary Care: Discomfort and injury of animals will be limited to that which is unavoidable in the conduct of scientifically valuable research.

3. Enrichment Strategy: Swine at the MREF may be given environmental enrichment toys, such as large balls, sealed PVC pipes with objects inside, kong toys, or large plastic toys.

   a. Dogs: NA

   b. Nonhuman Primates: NA

E. Data Analysis: For Phase II experiments, lethality and other quantal endpoints will be compared using Fisher's exact tests conducted at the five percent significance level. For continuous data, statistical comparisons are performed using either an ANOVA or a Student t-test conducted at the five percent significance level. Analyses may be performed on transformed data or using analogous nonparametric methods. If significant differences are found between baseline measurements of arterial or venous blood gases, heart rate or respiratory rate among the three groups of animals, then baseline measurements may be used as covariates in ANOVA.

F. Investigator & Technician Qualifications/Training: The Study Director is an experienced research veterinarian and toxicologist, and all animal technicians at the MREF are either AALAS certified as technicians or technologists or active in the

AALAS training program. Records of their experience and training are available at the MREF.

VIII. List of References

A. Castleman, W., Gillespie, J., Kosch, P., Schwartz, L., and Tyler, W. "The Role of Nonhuman Primates in Environmental Pollution Research", In Assessing Toxic Effects of Environmental Pollutants, S.D. Lee and J.B. Mudd., Eds. Ann Arbor, Michigan, (1979).

B. Diller, W.F., "Phosgene Induced Edema: Diagnosis and Therapeutic Countermeasure." In International Symposium on Phosgene Induced Edema: Diagnosis and Countermeasures, Mehlman, M.A., Fensterheim, R.J., Frosolono, M.F., eds., Princeton Scientific Publishing Co., Inc., Princeton, pp 7-15 (1985).

C. Mellick, P.W., Dungworth, D.L., Schwartz, L.W. and Tyler, W.S. Short Term Morphologic Effects of High Ambient Levels of Ozone on Lungs of Rhesus Monkeys. *Lab. Invest.* 36: 82-90 (1977).

D. Moore, S. and Gate, M. "Phosgene." In Chemical Warfare Agents and Related Chemical Problems. Washington, D.C., National Defense Research Committee, pp 17-29 (1946).

E. Rinehart, W.E. and Hatch, T. Concentration-Time Product (CT) as an Expression of Dose in Sublethal Exposure to Phosgene. *Indust Hygiene J.*, pp 545-553 (1964).

F. Urbanetti, J.S. Battlefield Chemical Inhalation Injury. In Pathophysiology and Treatment of Inhalation Injuries, J. Loke, ed. Marcel Dekker, New York (1988) .

G. Urbanetti, J.S. Phosgene: "Clinical Importance and Management." In Proceedings of the Workshop on Acute Lung Injury and Pulmonary Edema, sponsored by the USAMRICD, Aberdeen Proving Ground, Maryland(1989). ADA216293

H. AVMA, *1993 Report of the AVMA Panel on Euthanasia,* Journal of the American Veterinary Medical Association. Vol 202, No. 2, January 15, 1993, pgs 229-248.

I. National Research Council. *Guide for the Care and Use of Laboratory Animals.* Institute of Laboratory Animal Resources, Commission on Life Sciences, National

Research Council, National Academy Press, Washington, D.C. 1996.

IX. Biohazard/Safety:

A. General: Surety, security, and safety procedures for the use of chemical agents are thoroughly outlined in facility plans, in personnel requirements for qualification to work with the hazardous material and in standard operating procedures for storage and use of these materials.

B Compounds: Phosgene as a compressed gas will be purchased from a commercial source that will be identified in the study file and in the Final Report. The commercial source may supply the phosgene at required concentrations or at a selected concentration. The chemicals, hazardous wastes, agents, and agent wastes involved in this protocol will be handled in accordance with all applicable state and federal guidelines, regulations, and MREF SOPs to ensure that no significant adverse environmental effects occur.

X. Assurances:

A. Animal Use: The animals authorized for use in this protocol will be used only in the activities and in the manner described herein unless an amendment is specifically approved by the IACUC.

B. Duplication of Effort: I have made a reasonable, good faith effort to ensure that this protocol is not an unnecessary duplication of previous experiments.

C. Statistical Assurance: I assure that I have consulted with an experienced, well qualified statistician in the design and strategy of this study, and the minimum number of animals needed for scientific validity will be used.

D. Biohazard/Safety: I have taken safety into consideration in the design of this study and have made proper coordination in the preparation of this protocol.

E. Training: I verify that the personnel performing the animal procedures/manipulations described in this protocol are technically competent and have been properly trained to ensure that no unnecessary pain or distress will be caused as a result of the procedures/manipulations.

F. Responsibility: I acknowledge the inherent moral and administrative obligations

associated with the performance of this animal use protocol, and I assure that all individuals associated with this project will demonstrate a concern for the health, comfort, welfare, and well-being of the research animals. Additionally, I pledge to conduct this study in the spirit of the fourth "R" which the DOD has embraced, namely, "Responsibility" for implementing animal use alternatives where feasible, and conducting humane and lawful research.

Frances M. Reid
(Study Director)

G. Painful Procedures: I am conducting biomedical experiments which may potentially cause more than momentary or slight pain or distress to animals that will be relieved with the use of anesthetics. I have searched for alternatives to such procedures; however, I have determined that alternative procedures are not available to accomplish the objectives of the proposed experiment.

Frances M. Reid
(Study Director)

H. Scientific Review: Signature verifies that this proposed animal use protocol has received appropriate peer scientific review and is consistent with good scientific research practice.

(Signature Required) John D. Johnson
Research Unit Manager

I. Attending/Consulting Veterinarian: The attending/consulting veterinarian has reviewed the protocol and was consulted in the planning of procedures that require veterinary input, e.g., an unalleviated pain procedure. In addition, the veterinarian/veterinary medicine department has assisted with coordination for veterinary support to the protocol.

(Signature Required)
Attending/Consulting Veterinarian

J. Statistical Review: A person knowledgeable in statistics has reviewed the experimental design.

(Signature Required) Ronald G Mentzer

Study Statistician

XI. Records:

Records to be maintained include, but are not limited to:

A. Chemical analyses and exposure administration forms

B. Animal data

C. Clinical observations of animals

D. Histopathologic evaluations of pulmonary system

E. Miran or other analysis monitoring records.

XII. Reports:

A. A draft Final Report will be prepared within 30 working days after completion of the exposures and receipt of analyses of the data and histological data. The draft Final Report includes:

1. Names of key study personnel

2. Experimental design

3. Test material description, analyses, preparation, and administration

4. Clinical observations

5. Histopathologic evaluations of pulmonary samples

6. Statistical analyses of data

7. Discussions and conclusions.

B. Following receipt of comments on the draft final report from USAMRICD personnel, a final report will be prepared within 30 working days.

C. Interim results will be reported verbally to the COR during the course of the study as possible.

APPENDIX 1
EXPERIMENTAL DESIGN

Exposure/Time Group	Animal No.	Ventilation	PEEP	O_2%
I. Clean air/10 min	6	Yes	No	21
II. Phosgene/10 min	6	Yes	No	21
III. Phosgene/10 min	6	Yes	10 - 15	45

RESPIRATORY CASUALTY CARE MANAGEMENT IN THE FIELD
MEDICAL ENVIRONMENT

MREF Protocol 132. Amendment No. 1

Change Number (No.) 1

Change: Delete the following sentence under section VII. Materials and Methods D. 7. Euthanasia on page 15 of MREF Protocol 132.

> Animals will be euthanatized by an approved method as described in the 1993 Report of the AVMA Panel on Euthanasia, such as by an overdose of pentobarbital sodium (100 mg/kg) IV, or 1 mL/10 lbs of Beuthanasia® IV.

And replace with the following sentence.

> Animals will be euthanatized using an overdose of pentobarbital sodium (100 mg/kg) IV, or 1 mL/10 lbs of Beuthanasia® IV.

Reasons for Changes:

The change is made to clarify the euthanasia methods.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised.

Approved By:

Frances M. Reid — 9-15-97

Frances M. Reid, D.V.M. — Date
Study Director

Richard R Stotts — 15 SEP 97

Richard R. Stotts, D.V.M, Ph.D. — Date
USAMRICD
Contracting Officer's Representative

Registered by:

Elisha Morrison — 9/15/97

Elisha N. Morrison, M.S. — Date
Quality Assurance Specialist

Respiratory Casualty Care Management in the Field Medical Environment

MREF Protocol 132. Amendment No. 2

Change Number (No.) 1

Change: Delete the following sentence under section VII. Materials and Methods A. Experimental Design and General Procedures on page 7 of MREF Protocol 132.

> In Phase I, up to 5 animals will be exposed and monitored to determine the time course of specified endpoints which might be employed in the Phase II efficacy study.

And replace with the following sentence.

> In Phase I, up to 15 animals will be used to develop the anesthetic procedures and a minimum of 3 animals will be exposed and monitored to determine the time course of specified endpoints which might be employed in the Phase II efficacy study.

Reasons for Changes:

The change is made to add additional animals for Phase I to help develop the model.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised.

Change No. 2

Change: Delete the following paragraph under section VII. Materials and Methods B. Study Design 1. Phase I - Pilot Study on page 9 of MREF Protocol 132.

a. Up to five animals (Sus scrofa) will be used to select a phosgene exposure to be used in Phase II and to evaluate techniques to allow the pigs to be continuously anesthetized for up to three days. Animals will be anesthetized as described in section VII.D.1.b.(1). Animals will be catheterized, and exposed to concentrations of phosgene, using an initial exposure of 2000 $mg*min/m^3$. Depending upon results, an additional animal may be exposed to the same concentration or to an adjusted concentration. After each

exposure, the results will be evaluated by the Study Director in consultation with the Contracting Officer's Representative (COR) and Scientific Technical Objective (STO) Coordinator. Selected endpoints to be measured include, but are not limited to, impedance pneumogram, lethality (to include time interval to death), arterial and venous blood gases, heart rate, and respiratory rate (discussed in section VII. D. 6.). Lethality at 48 hr post-exposure is a primary endpoint. Up to two animals may be anesthetized and exposed per day, and they will be monitored 24 hr per day for up to 3 days.

And replace with the following paragraph.

a. Up to 15 animals (Sus scrofa) will be used to evaluate techniques to allow the pigs to be continuously anesthetized for up to three days and to select a phosgene exposure to be used in Phase II. Animals will be anesthetized as described in section VII.D.1.b.(1), catheterized, instrumented for monitoring animals as described below, and maintained anesthetized for 72 hr. Animals used to determine the phosgene challenge will be catheterized, instrumented, and exposed to concentrations of phosgene as determined by the client (an initial exposure to total 20,000 mg phosgene/m^3 over a 10 min exposure period. Depending upon results, additional animals may be exposed to the same concentration or to an adjusted concentration. After each exposure, the results will be evaluated by the Study Director in consultation with the Contracting Officer's Representative (COR) and Scientific Technical Objective (STO) Coordinator. Selected endpoints to be measured include, but are not limited to, impedance pneumogram, lethality (to include time interval to death), arterial and venous blood gases, heart rate, and respiratory rate (discussed in section VII. D. 6.). Lethality at 48 hr post-exposure is a primary endpoint. Up to two animals may be anesthetized and exposed per day, and they will be monitored 24 hr per day for up to 3 days (72 hr) before euthanasia.

Reasons for Changes:

The change is made to add additional animals for Phase I to help develop the model.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised.

Change No. 3

Change: Delete the following sentence under section VII. Materials and Methods C. Laboratory Animals Required and Justification 3. Laboratory Animals: e. Weight: on page 11 of MREF Protocol 132.

Approximately 16-20 kg (35-45 lbs) at dosing.

And replace with the following sentence.

Approximately 16-22 kg (35-48.4 lbs) at dosing.

Reasons for Changes:

The change is made to compensate for an estimated weight gain during each animal's in-house maintenance.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised.

Change No. 4

Change: Delete the following sentence under section VII. Materials and Methods D. Veterinary Care 1. Husbandry Considerations: b. Special Husbandry Considerations: Quarantine on page 17 of MREF Protocol 132.

Animals will be examined for evidence of disease and placed in quarantine for fourteen days.

And replace with the following sentence.

Animals will be examined for evidence of disease and placed in quarantine for seven days.

Reasons for Changes:

The change is made to eliminate the extra week of quarantine, since historic records with this vendor indicate animals appear to be healthy and do not require the additional quarantine time.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised.

Approved By:

Frances M. Reid — 3-18-98

Frances M. Reid, D.V.M. — Date
Study Director

Richard R. Stotts — 15 April 98

LTC Richard R. Stotts, D.V.M, Ph.D. — Date
USAMRICD COR

Registered by:

Elisha Morrison — 6/29/98

Elisha N. Morrison, M.S. — Date
Quality Assurance Specialist

Respiratory Casualty Care Management in the Field Medical Environment

MREF Protocol 132. Amendment No. 3

Change Number (No.) 1

Change: Replace Ron Menton as the Study statistician in MREF Protocol 132 section II. Co-Investigators: A. Study Statistician and as statistical reviewer for this protocol with Nancy Niemuth. Replace Bruce Johnson as Scientific Reviewer with Jim Estep in MREF Protocol 132.

Reasons for Changes:

Ron Menton and Bruce Johnson are no longer at Battelle and Protocol 132 responsibilities have been given to Nancy Niemuth.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised.

Change No. 2

Change: Replace the sentences describing anesthetic procedures relating to the use of atropine and a pentobarbital sodium drip anesthetic under the following sections VII. A. Experimental Design and General Procedures, General Procedures: on page 6 first paragraph and section VII. D. 1. b. (1) Anesthesia/Analgesia/Tranquilization: on page 12,

With the following:

Animals will be anesthetized with an appropriate anesthetic regimen. The anesthetic regimen developed will be documented in the study file and final report. The anesthetic regimen developed will allow the placement of femoral catheters, and if different from a drip-type anesthetic, will result in a smooth transition to an appropriate drip-type anesthetic. An example of one such regimen is Isoflurane anesthetic administered during catheter placement and weaned to a pentobarbital sodium drip. Atropine may be given subcutaneously (SQ) to counteract excessive secretory responses and to decrease peristalsis (Castleman et al, 1979), if determined necessary by the study director or after consultation with a staff veterinarian. An eye ointment will be administered

periodically on an as needed basis.

Reasons for Changes:

The change is made to clarify the need to develop an anesthetic regimen that would enhance the survivability of the animals for 72 hours. The veins for catheter placement are deeper in swine and require surgical cutdown to insert the catheter. Surface veins were not of sufficient size to receive the slow infusion/drip of pentobarbital sodium without causing irreversible damage to the vein. The study director in consultation with the Contract Officer's Representative, and USAMRICD's Technical Point of Contact determined that the use of Isoflurane would not be expected to affect the parameters being measured. Although there is potential to affect the ventilation of the animal, most of the Isoflurane will have been expired and all animals are treated the same way. Animals given atropine developed mucus deposits in the trachea which were difficult to remove from the tracheal tube. Therefore, atropinization of the animal was removed as a variable that could affect the study.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised. Removal of Atropine administration is expected to improve the study, by reducing a variable.

Change No. 3

Change: Delete the references to the use of gas chromatography (e.g., GC-FID) under section VII. A., Exposure System Design and Characterization: on page 7 of MREF Protocol 132 and delete the exposure system figure on page 8.

Reasons for Changes:

The change is made to reflect a decision by the study director after consultation with the MREF chemist, Battelle's inhalation exposure system engineer, the Contract Officer's Representative, and USAMRICD's Technical Point of Contact, that use of gas chromatography was not necessary for this study and will not be done. Time needed to develop the technique and validate the system was not available. The final exposure system schematic will be in the final report. This exposure system has been modified to correct problem areas experienced during set-up and validation.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised. The Miran provided sufficient data for the conduct of the study and a redundant method was not necessary. The exposure system adjustments simplified the system and reduced pressure in the system against which a ventilated animal would breath.

Change No. 4

Change: Delete the reference to initial phosgene exposure of 2000 mg.min/m^3 under section VII. B. 1. a. on page 9 of MREF Protocol 132 (as amended by amendment 2, page 26, change 2), and change the 3rd sentence to read:

Animals used to determine the phosgene challenge will be catheterizecd, and exposed to concentrations of phosgene. An initial concentration of 1000 mg/m^3 for 10 min may be used as the initial exposure or alternate exposure concentration recommended by the Technical Point of Contact.

Reasons for Changes:

The change is made after review of data provided by the Technical Point of Contact and consultation with USAMRICD personnel with previous phosgene exposure experience recommended the initial exposure be 1000 mg/m^3 for 10 min.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised. Data indicated the 2000 mg.min/m^3 might be too low or too high to achieve the desired endpoint of no survivability within 24 hr.

Change No. 5

Change: Delete references to venous blood gases as samples for collection or endpoints to be measured in the following sections: VII. B. 1. a. sixth sentence of first paragraph on page 9 (as amended by amendment 2, page 26, change 2); VII. D. 4. b. Biosamples first sentence on page 14; and VII. D. 6. Study Endpoints first sentence on page 15.

Reasons for Changes:

Discussion with the Technical Point of Contact concerning the venous blood data, indicated that this data did not provide added benefit. The arterial data provided greater benefit. Additional time points could be collected for arterial blood if needed by eliminating the venous blood samples.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised. The study would be improved by adding additional time points to the arterial blood data.

Change No. 6

Change: Delete the second sentence on page 15, section VII.D.1.a. referring to the 1 hr delay in removing the animal from the fume hood.

Replace with:

Animals may be removed from the hood when it is determined there is no threat of phosgene exposure. The method of determination will be in the study file and approved of by Battelle's Environmental, Health, and Safety Officer.

Reasons for Changes:

During the validation of the exposure system, data was collected that indicated phosgene was not detected within the system in less than 2 minutes. When animal exposures were conducted, phosgene detection was below the level of detection in less than 2 minutes. The study director on the recommendation, and with the data collected, obtained approval from MREF's Environmental, Health, and Safety Officer to remove the animal from the chemical fume hood after 2 minutes post-exposure of flushing the system with room air.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised.

Change No. 7

Change: Change the Lettering on sections VII. D. Veterinary Care:, VII. E. Data Analysis:, and VII. F. Investigator & Technician Qualifications/Training: on pages 15, 18, and 18 respectively, to VII. E. Veterinary Care:, VII. F. Data Analysis:, and VII. G. Investigator & Technician Qualifications/Training:

Reasons for Changes:

The outline lettering was duplicated for the letter D. Clarity of the protocol outline and location of sections was enhanced by changing the outline lettering.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised.

Change No. 8

Change: Delete the last sentence of section VII. E. b. Anesthetization, Exposure and After Exposure: referring to IV nutrients discussed on page 16 of Protocol 132.

Replace with: IV fluid therapy will be instituted after catheterization of the animal and during the course of the study. The type, amount and method of delivery will be determined in Phase I and documented in the study files and final report.

Reasons for Changes:

Consultation with various veterinary swine and critical care specialist indicated that neither lipid, nor amino acid supplementation were expected to be necessary during the 72 hr chemical restraint. At a minimum, lactated Ringer's solution was recommended for administration over the 72 hr period. Administration of additional nutrients was thought to be unnecessary.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised.

Change No. 9

Change: Revise protocol 132 (pages 7 and 9) where references to animal numbers and Phase II treatment groups are discussed. Add five animals for range finding studies, six animals for therapy control group and two treatment groups of six animals each to Phase II. A detailed description under Study Design heading follows below.

Reasons for Changes:

Several compounds have been identified in rodent and rabbit screens to be effective in the treatment of phosgene exposure. The pig model established at Battelle provides a higher species with a cardiovascular system similar to humans and is a practical model designed to test therapeutic regimens in a 72 hr anesthetized ventilated pig model.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised. The additional animals are required to identify an appropriate exposure concentration for phosgene. The addition of the two treatment groups will enhance the study.

Study Design - revised:

In phase I, up to five additional animals may be used to identify a phosgene exposure concentration or used as replacement animals. Procedures and methods developed with the model to date will apply to these animals.

In phase II, five groups with six swine in each are used to determine the efficacy of PEEP, Ibuprofen, and another treatment group such as N-acetyl-cysteine (20 percent,purchased from a commerical source to be determined), against pulmonary edema induced by phosgene inhalation. An additional treatment group of three animals per compound will be added as control animals for ibuprofen and N-acetyl-cysteine. Treatment groups will be randomized using a Latin Square Arrangement and documented in the study file.

The following treatment groups will be evaluated:

a. 6 swine exposed to clean air;
b. 6 swine exposed to phosgene concentration as determined in Phase I

c. 6 swine exposed to phosgene concentration as determined in Phase I followed by immediate positive pressure ventilation and respiratory assistance.

d. 6 swine exposed to phosgene concentration as determined in Phase I followed by Ibuprofen. The treatment regimen is to be determined.

e. 6 swine exposed to phosgene concentration as determined in Phase I followed by acetyl-cysteine (Mucosil). The treatment regimen is to be determined.

f. 6 swine exposed to clean air with 3 receiving ibuprofen and 3 receiving N-acetyl-cysteine

Animals will be anesthetized, mechanically ventilated and exposed to either clean air or a phosgene concentration selected from Phase I data. Physiologic endpoints selected from Phase I data are monitored. The treatment regimens for Ibuprofen and N-acetyl-cysteine will be provided by the Technical Point of Contact at USAMRICD. Commercial formulations will be used where available. If these formulations need preparation for administration to swine, then MREF's chemistry staff will conduct the preparation after consultation with Technical Point of Contact at USAMRICD. The level of PEEP and oxygen respiratory assistance will be determined based on medical references and the final recommendation for the Phase II study design approved by the study director, COR and Technical Point of Contact at USAMRICD. The procedures and methods developed in Phase I to use in Phase II will be documented in the study file and final report. Anesthetized animals may be monitored for up to 3 days if this is determined to be necessary by the Study Director in consultation with the COR and Technical Point of Contact.

Data collected for the treatment groups will be those determined in Phase I. At a minimum, the primary endpoints for treatment comparison will be the time interval to death from the end of the phosgene exposure, the mean wet/dry lung weight ratios, and partial pressure of oxygen in arterial blood (PO_2).

Additional control animals (maximum of 6) may be needed for evaluation of the two additional treatment groups. Three animals per compound may be included in the current Phase III study design. These control animals will be evaluated using the same study procedures and monitored as the air only control group and will receive either ibuprofen or N-acetyl-cysteine treatment.

Experimental Design

Exposure/Time Group	Animal No.	Ventilation	PEEP	O_2%	Ibuprofen	N-acetyl-cysteine
I. Clean air/10 min	6	Yes	Physiological 5	30	NA	NA
II. Phosgene/10 min	6	Yes	Physiological 5	30	NA	NA
III. Phosgene/10 min	6	Yes	10 - 15	45	NA	NA
IV. Phosgene/10 min	6	Yes	Physiological 5	30	Yes	NA
V. Phosgene/10 min	6	Yes	Physiological 5	30	NA	Yes
VI. Clean Air/10 min	3/tx compound	Yes	Physiological 5	30	Yes –3 An	Yes –3 An

Approved By:

Frances M. Reid — 9-9-98
Frances M. Reid, D.V.M. — Date
Study Director

Richard R. Stotts — 13 Nov 98
LTC Richard R. Stotts, D.V.M, Ph.D. — Date
USAMRICD COR

Registered by:

Elisha N. Morrison — 11/24/98
Elisha N. Morrison, M.S. — Date
Senior Quality Assurance Specialist

RESPIRATORY CASUALTY CARE MANAGEMENT IN THE FIELD MEDICAL ENVIRONMENT

MREF Protocol 132. Amendment No. 4

Change Number (No.) 1

Change: On page 35, at the end of the last paragraph, add the following sentence.

"The order of exposures determined by the Latin Square for the first animals from each treatment group may not be followed as stated."

Reasons for Changes:

Due to contract time constraints, dose-response estimates based on single animal results, and results differing from what was expected, treatment order may change to allow more time to evaluate exposure and/or treatment data and literature search results.

Impact on the Study:

There are no adverse affects on the study nor is the integrity of the study compromised. By altering exposure order when necessary, the Study Director will have additional time to determine the appropriate treatment dose and regimen, and still meet contract time constraints.

Change Number (No.) 2

Change: On page 11, VII.C.4. Total number of animals required:

Change the total number of animals required to 70 and include the statement "The final total number of animals used will be reported in the Final Report."

Reasons for Change:

Additional animals are needed to identify a phosgene challenge dose, to add 3 treatment groups and determine a treatment dose range for these groups, and as replacement animals.

Impact on Study:

There are no adverse effects on the study nor is the integrity of the study compromised.

Change Number (No.) 3

Change: On page 12, VII.D.1.a.(2) Alleviated Pain – Column D. Change the number 23 to 70 (100%) and include the statement: "Animals used in this study will fall in this category. The total number of animals used will be reported in the Final Report.

Reasons for Change:

Additional animals are needed to identify a phosgene challenge dose, to add 3 treatment groups and determine a treatment dose range for these groups, and as replacement animals.

Impact on Study:

There are no adverse effects on the study nor is the integrity of the study compromised.

Approved By:

Frances M. Reid, D.V.M.
Study Director

11-25-98
Date

LTC Richard R. Stotts, D.V.M, Ph.D.
USAMRICD COR

1 DEC 98
Date

Registered by:

Elisha N. Morrison, M.S.
Senior Quality Assurance Specialist

2/12/99
Date

ATTACHMENT B

NORMAL CLINICAL CHEMISTRY AND PHYSIOLOGY VALUES AND ADJUSTABLE PARAMETERS CHART

Table B.1.a. Normal Values for Respiratory Gases and Selected Physiological Measurements

Measurements	Normal Range
Expired Carbon Dioxide (%)	32-45
Inspired Oxygen (%)	21-30
Oxygen Saturation (%)	>90
Pulse Rate (beats per min, bpm)	70-120[a]
Systolic Blood Pressure (mm Hg)	100-160[a]
Diastolic Blood Pressure (mm Hg)	60-100[a]
Mean Blood Pressure (mm Hg)	80-120[a]
Respiratory Rate (breaths per min)	20-40[a]
Impedance (IMP, ohms)	NA

[a] Measured in conscious animals

Table B. 1. b. Normal Values for Hematology and Clinical Chemistry Measurements

Measurements	Normal Range
Sodium (mmol/L)	135-150
Potassium (mmol/L)	3.5-5.5
Chloride (mmol/L)	88-115
Blood Urea Nitrogen (mg/dL)	8-24
Glucose (mg/dL)	82-113
pH	7.35-7.45
Partial Pressure of CO_2 (mm Hg)	35-45
Partial Pressure of O_2 (mm Hg)	80-110
Bicarbonate Ion (mmol/L)	22-27
Total CO_2 (mmol/L)	26.4
Base Excess (mmol/L)	2.8
Anion Gap (mmol/L)	10-25
Hemoglobin (g/dL)	10-16
Hematocrit (%)	32-50

Table B.2. Selected Parameters with Acceptable Ranges and Adjustments

Measurement	Acceptable Range	Adjustments
SpO_2	90-100 %	If < 90, check OxyTip sensor or ↑ O_2 (oxygen concentrator) up to 30% for control pigs and 45 % for phosgene-exposed pigs.
Expired O_2	35-40 %	If < 30, ↓ RR. If > 45, ↑ RR or think about perfusion/ventilation problems.
Inspiratory O_2*	21-22 %	If ↓, increase use of oxygen concentrator.
Impedance	15-20 ohms	Expect ↓ with pulmonary edema. If unexpected ↓, check attachments or bands.
Heart Rate	80-120 bpm	If < 80, decrease pentobarbital.
Respiratory Rate*	20-40 brpm in conscious animals	If < 8 brpm, assess anesthesia depth, ↑ ventilator R if anesthesia is ok. I > 10 brpm, assess anesthesia depth, ↓ ventilator RR if anesthesia is ok.
Blood Pressure	80-120/50 – 80 mm Hg	If unexpected ↓, check catheter patency.
Lactated Ringer's Solution*	45 mL/hr	If ↑ in lung sounds, ↓ flow rate (down to 25 mL/hr).
Pentobarbital	~ 3 mL/hr	If getting light, can ↑ rate or give 0.5-1.5 mL Pentobarbital i.v. If going deep, ↓ rate or stop pentobarbital Adm./call veterinarian.
Hematocrit	30-40 % PCV	Adjust i.v. fluids intake
Arterial Blood pH	7.4	If ↑, sodium bicarbonate adjust/ ↑ RR If ↓, sodium bicarbonate adjust/↓ RR
Potassium	3.5-5.5 mmol/L	If ↑, administer Ca glucogon i.v. If ↓, add potassium at 20-40 mEq/L to fluids.
Urine Flow	35 mL/kg/day	If ↓, increase fluids.
Lung Fluid	None	If ascultated, decrease i.v. fluid.

*Parameters with established settings

Animal Number._____ Date:_____

Diagram of the Swine Lung
Task G1555-48A
P.I. Dr. F. Reid

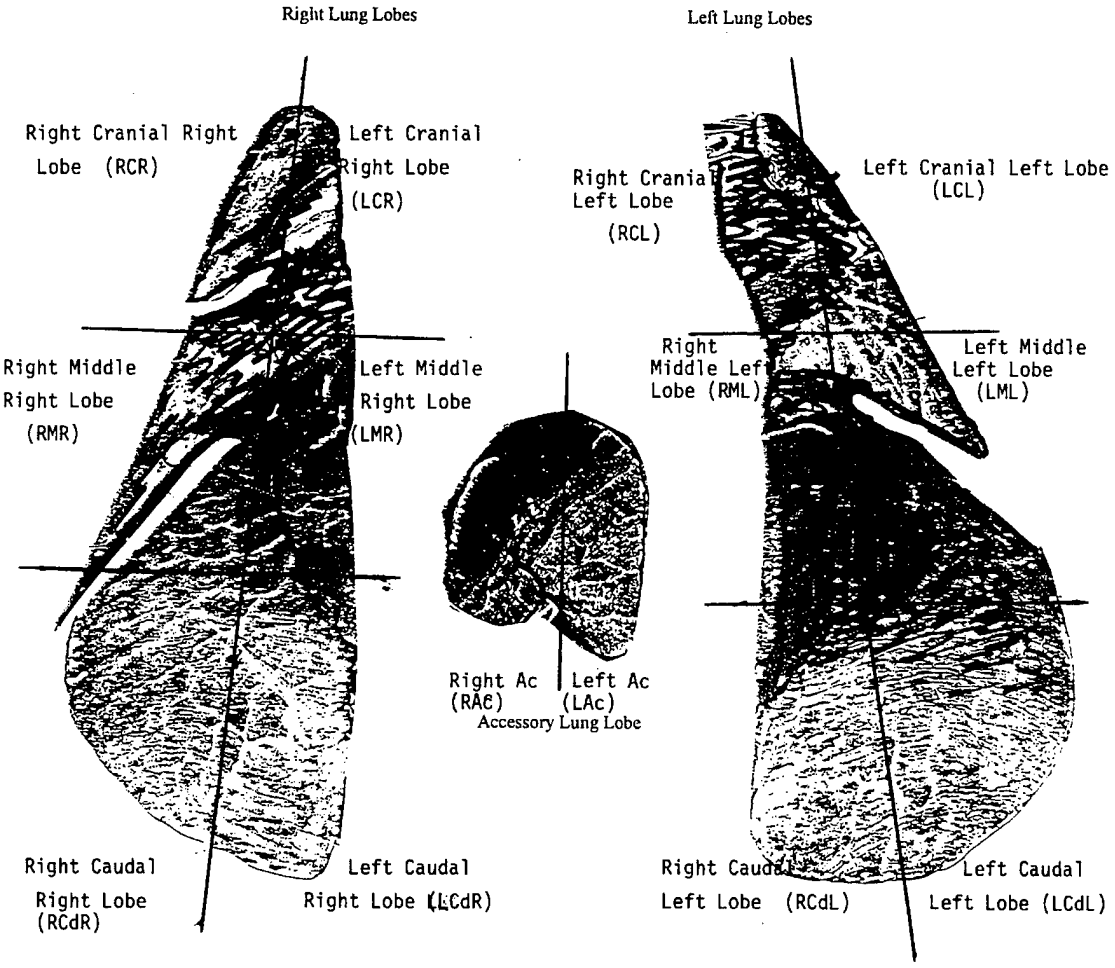

FIGURE B.1. DIAGRAM OF SWINE LUNG SECTIONS

ATTACHMENT C

PHOSGENE AND AIR EXPOSURE SYSTEM REPORT

Task 48
Phosgene Exposure System Report

Objective

The objective was to expose pigs to controlled concentrations of phosgene vapor over a 10-minute period.

Approach

A mixture of 1% phosgene gas with balance nitrogen (Matheson Co., Twinsburg, OH) was diluted with air to achieve the desired phosgene concentration. The phosgene challenge was delivered to the pig via a Harvard Ventilator Model 613 (Harvard Apparatus, Holliston, MA). A Miran 1B2 single beam infrared (IR) spectrometer (Foxboro Company, Foxboro, MA) was used to quantify the phosgene concentration.

Test Setup

This system was designed to operate in four modes: Miran Closed-Loop Calibration, Flowthrough Characterization, Animal Exposure, and Characterization of Delivered Concentration. A description of the operation in each mode is discussed below. A photograph of the system is shown in Figure 1 and schematics of the exposure and degradation assessment systems are shown in Figures 2 and 3, respectively.

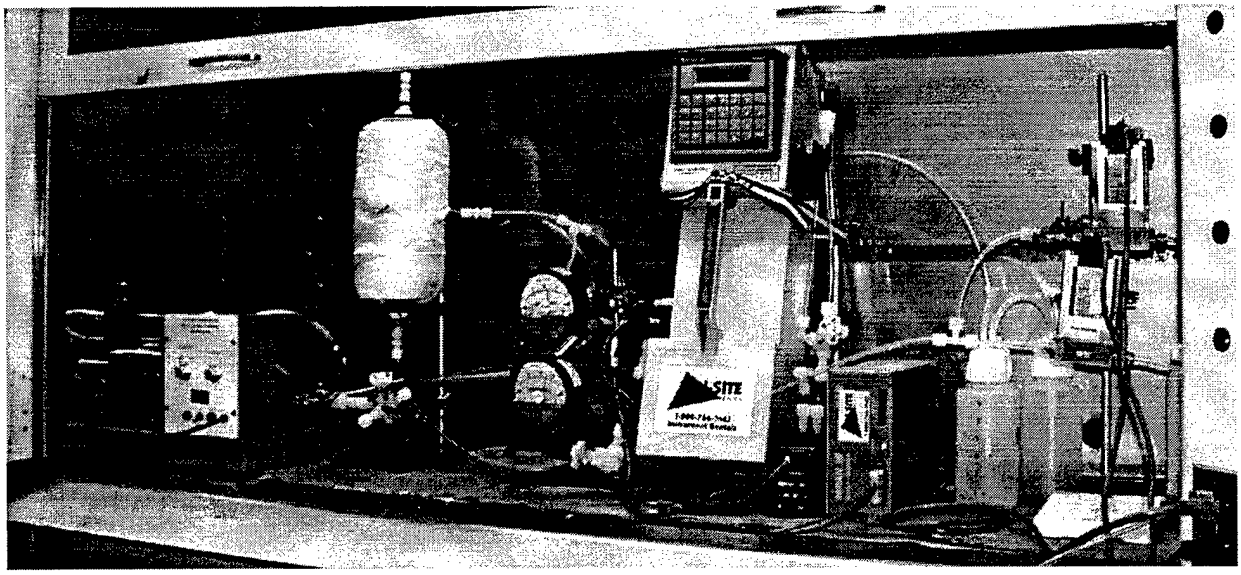

Figure 1. Photograph of Exposure System

Miran Closed-Loop Calibration Mode

In the Miran closed-loop calibration mode, calibrated volumes of 1% phosgene gas with a concentration of 40,477 mg/m^3 were introduced through the septum in the closed loop calibration system that has an internal volume of 3.44 liters. The resulting phosgene concentrations covered a range around the target exposure concentration. The phosgene concentration ([$COCl_2$]) within the closed loop system was calculated using the following equation:

$$[COCl_2]\left(\frac{mg}{m^3}\right) = \frac{COCl_2\ Injection\ Volume\ (ml)\ x\ 40{,}477\left(\frac{mg}{m^3}\right)}{3{,}440\ (ml)}$$

A MB-41 Metal Bellow pump (Senior Flexonics Inc., Sharon, MA) circulated the phosgene/air mixture through the Miran. Miran inlet pressure was monitored for later correlation with the flowthrough and exposure Miran output. The inlet pressure during the closed-loop calibrations was typically slightly above ambient pressure (744 mm Hg), while the inlet pressure during flowthrough calibration and animal exposure were typically around 791 and 782 mm Hg, respectively. The Miran output was then plotted versus the known phosgene concentration and a second order curve was fit to the data. This regression along with the inlet pressure was used to calculate the phosgene concentrations. Closed-loop calibrations were performed before and after every exposure to ensure accurate characterization of the exposure.

To ensure that the exposure system was functioning within acceptable limits, an acceptance criteria was established for the Miran output during closed loop calibrations. The criteria is described in Attachment 1.

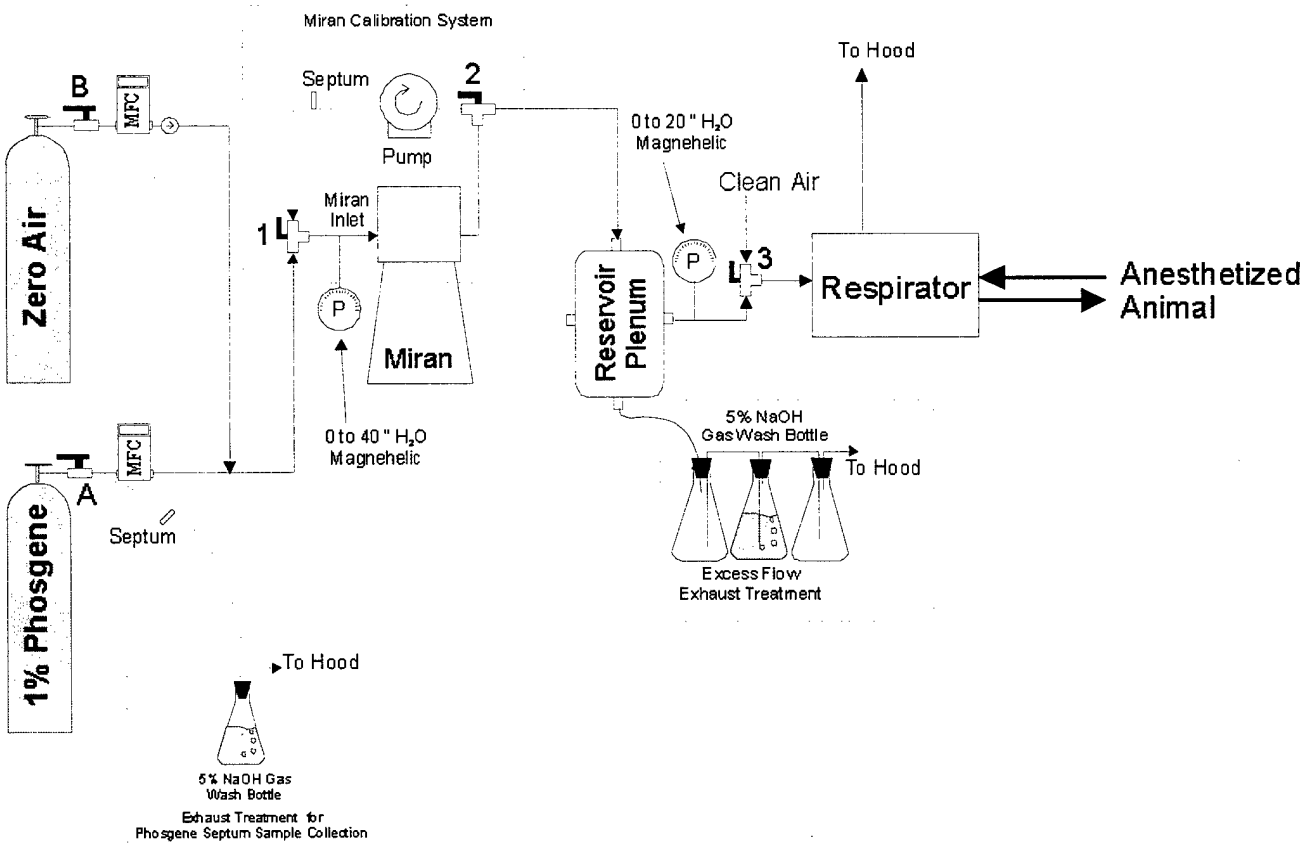

Figure 2. Schematic of Phosgene Exposure System

Flowthrough Characterization Mode

In the flowthrough characterization mode, Model FC 280 Tylan mass flow controllers (MFC, Tylan General, Salem, NH) were used to control the mixing ratio of 1% phosgene gas and clean

air. Both gases originated from pressurized gas cylinders and the MFC head pressure was set to 25 and 40 psig for the phosgene and air cylinders, respectively. The combined flow was directed through the pre-calibrated Miran to quantify the phosgene concentration. The flow was then directed into a reservoir plenum and then exhausted through a gas wash bottle containing a 5% sodium hydroxide (NaOH) solution in water (Attachment 2 describes the phosgene decontamination efficiency of the 5% NaOH solution). Prior to exposing the animal, the phosgene and air flows were set to achieve the Miran output corresponding to the desired exposure concentration identified during the closed-loop calibration after correction for pressure difference. The following equation was used to scale the increased pressurized flowthrough Miran output to the unpressurized closed loop calibration.

$$Closed\text{-}Loop\ Miran\ Output = Flowthrough\ Miran\ Output\ x \left(\frac{Closed\text{-}Loop\ pressure\ (mm\ Hg)}{Flowthrough\ pressure\ (mm\ Hg)} \right)$$

Animal Exposure Mode

In the animal exposure mode, the three-way valve going from the reservoir plenum to the ventilator was opened allowing the Harvard to intermittently draw a portion of the flow and deliver it to the anesthetized pig. The exhalation exhaust from the pig was vented to the back of the hood. Each exposure lasted 10 minutes. The Miran output and inlet pressure were recorded at 1-minute intervals.

Characterization of Delivered Concentration Mode

The objective of characterizing the delivered concentration was to verify the phosgene exposure concentration. To accomplish this, the system was operated in the flowthrough mode at the same MFC settings used during the animal exposure and the Miran output and inlet pressure were recorded. The system was then flushed with clean air and reconfigured as illustrated in Figure 3 so the Miran monitored the phosgene concentration that was delivered to the intra-tracheal tube. The animal exposure MFC settings were set and the Miran output and inlet pressure was recorded. The Miran output was then scaled based on pressure and the calculated phosgene concentrations were compared with those calculated during animal exposure mode.

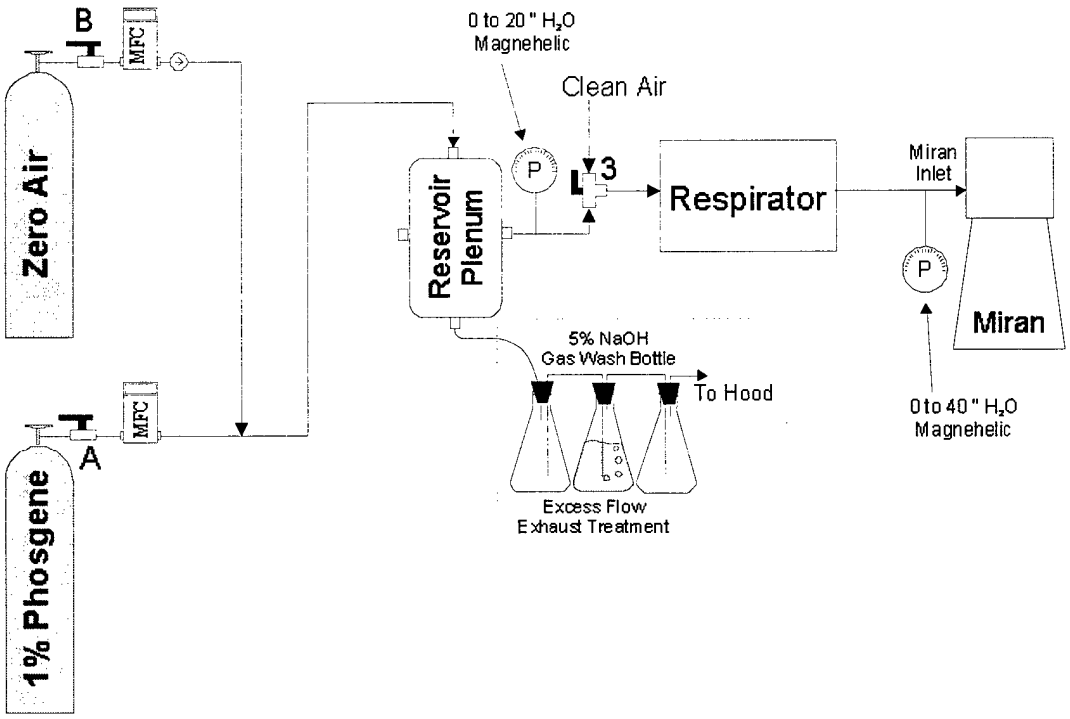

Figure 3. Phosgene Degradation Assessment System

Results

As stated above, the Miran was calibrated before and after each test and the reported exposure concentration was calculated from the averaged calibration values and the difference in system pressure between the closed-loop calibration and the exposure. During all testing, the Miran wavelength was set to 11.98 μm and pathlength to 0.75 m. Table 1 summarizes the closed-loop calibration results for all tests with a 450 mg/m^3 target exposure concentration, excluding Tests 39 and 41 (see Attachment 1 for explanation on data omission). Figure 4 is a plot of the same closed-loop calibration data. The minor variations in calibration data (± 4% in Miran output) are well within the expected system noise.

Table 1. Averaged Closed-Loop Results for 450 mg/m^3 Exposure Tests

Injected Volume (ml)	Phosgene Calibration Conc. (mg/m3)	Miran Output (average ± σ)
33	388	0.1350 ± 0.0023
38	447	0.1537 ± 0.0025
43	506	0.1723 ± 0.0028

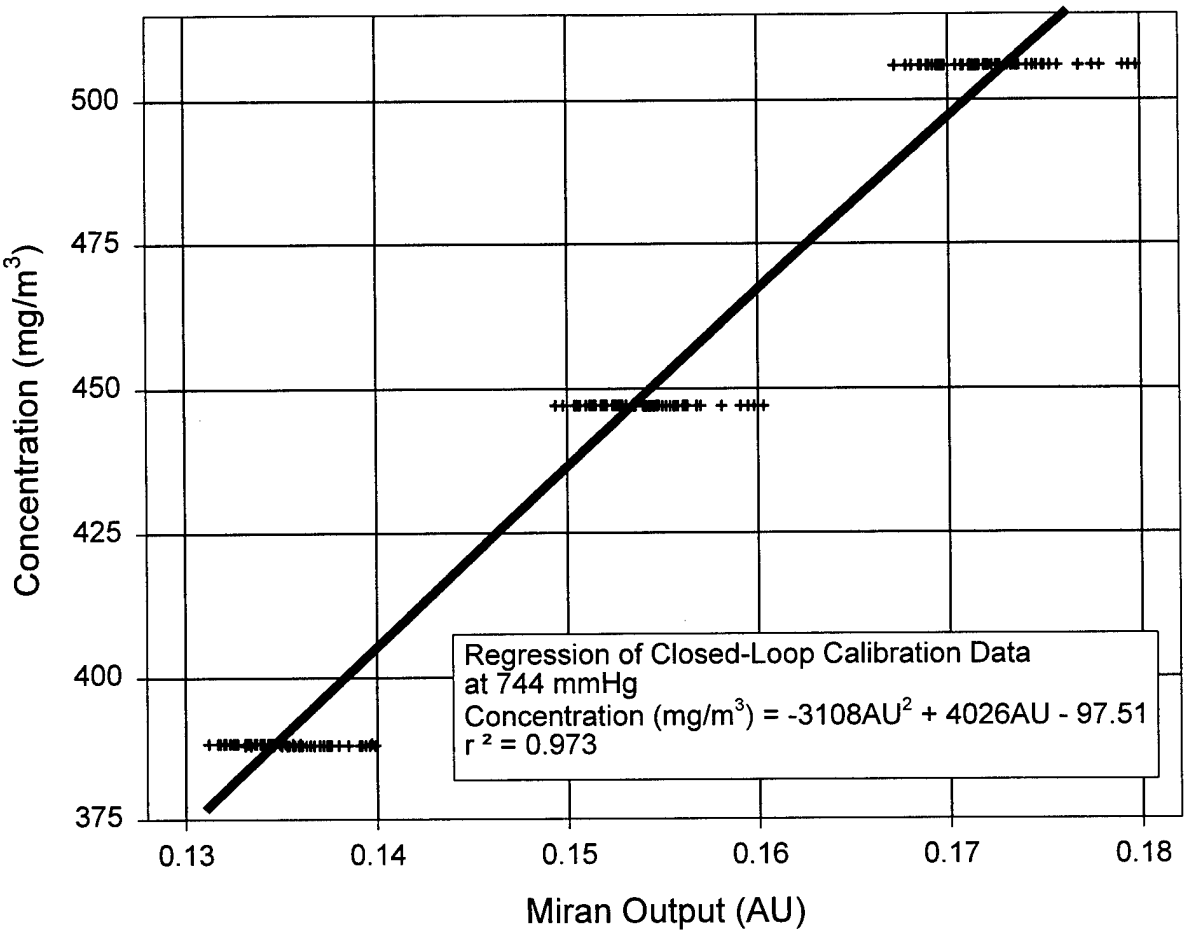

Figure 4. Closed-Loop Calibration Data

Table 2 lists the 65 exposure tests that were performed. The first 14 exposure tests were used to determine the target exposure level. After Test 15, all phosgene exposure tests had the same target exposure concentration of 450 mg/m^3. There were a total of 30 tests at the 450 mg/m^3 exposure concentration (including Tests 39 and 41).

Table 2. Summary of Exposure Tests Performed

Test #	Date	Phosgene Conc. (mg/m^3)		Exposure Times			Exposure (mg·min/m^3)	Pig ID
		Target	Actual	Start (h:m)	Stop (h:m)	Dur. (min)		
1	22-Jun-98	1,000	937	12:17	12:27	10	9,370	98-45-3
2	29-Jun-98	250	Animal died prior to exposure.					98-44-3
3	7-Jul-98	250	245	11:49	11:59	10	2,450	98-51-3
4	13-Jul-98	500	493	11:33	11:43	10	4,930	98-50-7
5	21-Jul-98	375	371	12:38	12:48	10	3,710	98-55-1
6	3-Aug-98	325	329	11:32	11:42	10	3,290	98-60-2
7	17-Aug-98	375	377	11:43	11:53	10	3,770	98-33-3
8	31-Aug-98	550	557	11:37	11:47	10	5,570	98-48-6

Test #	Date	Phosgene Conc. (mg/m^3)		Exposure Times			Exposure (mg·min/m^3)	Pig ID
		Target	Actual	Start (h:m)	Stop (h:m)	Dur. (min)		
9	14-Sept-98	425	425	11:37	11:47	10	4,250	98-104-6
10	21-Sept-98	0	0	11:32	11:42	10	0	98-110-2
11	12-Oct-98	425	Animal died prior to exposure.					98-114-1
12	26-Oct-98	425	420	11:28	11:38	10	4,200	98-18-5
13	2-Nov-98	500	491	11:47	11:57	10	4,910	98-116-3
14	9-Nov-98	500	497	11:33	11:43	10	4,970	98-116-1
15	16-Nov-98	450	453	11:19	11:29	10	4,530	98-116-2
16	23-Nov-98	450	449	11:24	11:34	10	4,490	98-213-1
17	30-Nov-98	0	0	10:55	11:05	10	0	98-220-3
18	7-Dec-98	450	449	11:07	11:17	10	4,490	98-221-6
19	14-Dec-98	450	446	11:51	12:01	10	4,460	98-222-6
20	28-Dec-98	450	452	11:14	11:24	10	4,520	98-232-2
21	4-Jan-99	0	0	11:15	11:25	10	0	98-236-6
22	12-Jan-99	0	0	11:54	12:04	10	0	98-241-1
23	12-Jan-99	450	449	14:47	14:57	10	4,490	98-241-6
24	18-Jan-99	450	453	10:45	10:55	10	4,530	98-247-1
25	18-Jan-99	450	453	13:00	13:10	10	4,530	98-249-1
26	25-Jan-99	450	450	11:54	12:04	10	4,500	99-246-1
27	25-Jan-99	450	450	14:22	14:32	10	4,500	99-249-5
28	1-Feb-99	0	0	11:30	11:40	10	0	99-253-1
29	1-Feb-99	450	456	14:42	14:52	10	4,560	99-253-3
30	8-Feb-99	0	0	11:35	11:45	10	0	99-251-6
31	8-Feb-99	450	450	13:33	13:43	10	4,500	99-255-3
32	15-Feb-99	0	0	11:49	11:59	10	0	99-256-1
33	15-Feb-99	450	447	14:36	14:46	10	4,470	99-256-4
34	22-Feb-99	450	450	11:07	11:17	10	4,500	99-259-1
35	22-Feb-99	450	456	13:06	13:16	10	4,560	99-259-2
36	1-Mar-99	0	0	10:57	11:07	10	0	99-260-2
37	1-Mar-99	450	449	12:46	12:56	10	4,490	99-262-3
38	3-Mar-99	0	0	10:40	10:50	10	0	99-263-2
39	3-Mar-99	450	458	13:19	13:29	10	4,580	99-263-1
40	29-Mar-99	0	0	10:55	11:05	10	0	99-272-2
41	29-Mar-99	450	430 to 500	13:01	13:11	10	4,300 to 5,000	99-272-3
42	5-Apr-99	0	0	10:38	10:48	10	0	99-21-1
43	5-Apr-99	450	449	12:35	12:45	10	4,490	99-21-2
44	12-Apr-99	0	0	10:54	11:04	10	0	99-272-5
45	12-Apr-99	450	451	12:50	13:00	10	4,510	99-272-4
46	3-May-99	0	0	11:23	11:33	10	0	99-111-3
47	3-May-99	450	449	13:13	13:23	10	4,490	99-111-4

Test #	Date	Phosgene Conc. (mg/m^3)		Exposure Times			Exposure (mg·min/m^3)	Pig ID
		Target	Actual	Start (h:m)	Stop (h:m)	Dur. (min)		
48	10-May-99	0	0	10:36	10:46	10	0	99-288-4
49	10-May-99	450	452	13:59	14:09	10	4,520	99-92-6
50	17-May-99	0	0	10:46	10:56	10	0	99-293-2
51	17-May-99	450	451	13:19	13:29	10	4,510	99-294-3
52	24-May-99	0	0	10:39	10:49	10	0	99-298-2
53	24-May-99	450	451	12:51	13:01	10	4,510	99-298-1
54	1-Jun-99	0	0	10:24	10:34	10	0	99-287-1
55	1-Jun-99	450	451	12:39	12:49	10	4,510	99-287-2
56	7-Jun-99	0	0	10:30	10:40	10	0	99-31-5
57	7-Jun-99	450	448	12:25	12:35	10	4,480	99-31-3
58	21-Jun-99	0	0	10:10	10:20	10	0	99-41-4
59	21-Jun-99	450	450	12:59	13:09	10	4,500	99-140-1
60	28-Jun-99	0	0	10:26	10:36	10	0	99-146-3
61	28-Jun-99	450	450	12:39	12:49	10	4,500	99-147-2
62	6-Jul-99	0	0	10:16	10:26	10	0	99-136-1
63	6-Jul-99	450	447	13:22	13:32	10	4,470	99-136-6
64	12-Jul-99	0	0	10:26	10:36	10	0	99-150-3
65	12-Jul-99	450	451	13:05	13:15	10	4,510	99-153-3

Analysis of Exposure Data

The following analysis was performed only on those tests in which the target exposure level was 450 mg/m^3. Tests 39 and 41 were excluded based on the analysis provided in Attachment 1.

The exposure concentrations were consistently within 2% of the 450 mg/m^3 target (Figure 5).

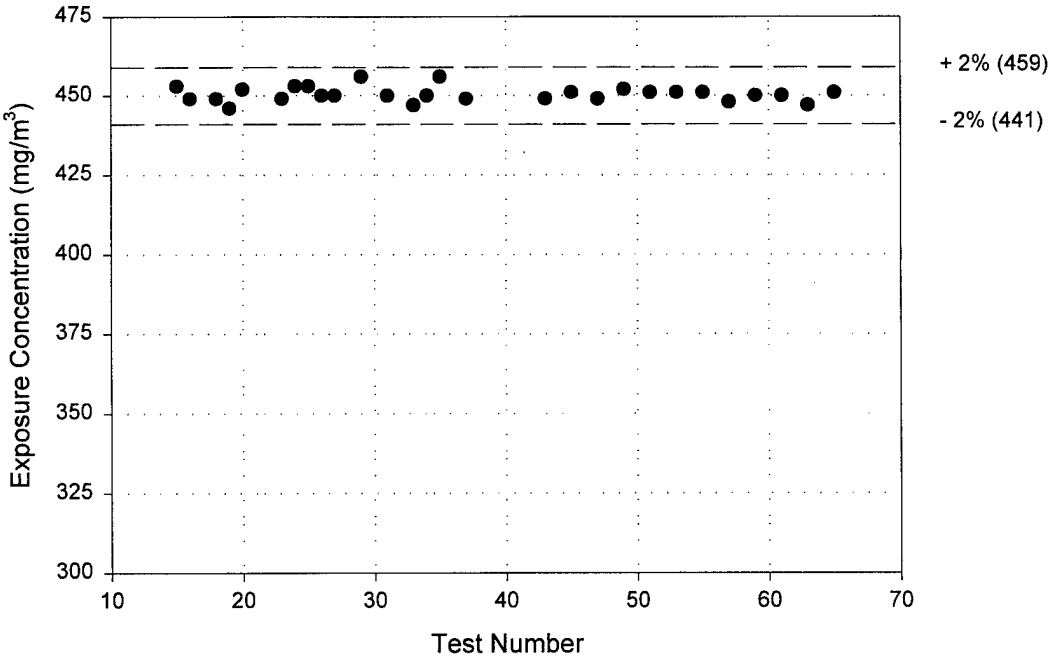

Figure 5. Actual Exposure Concentrations for 450 mg/m^3 Target Exposure Tests

Additional Exposure System Analysis

During the project, there were concerns that the water reactive phosgene exposure had to pass through a high humidity section of Tygon® tubing prior to being inhaled by the animal. This was part of the respirator to endotracheal tubing section. During most, if not all exposure tests, water droplets formed on the inner wall of this post-endotracheal tubing section due to animal exhalation. If a significant percentage of the phosgene exposure had been degraded, the reported exposures may have been overstated.

To address this concern, a study was performed that documented that the wetted post-endotracheal Tygon® tubing section causes negligible degradation in phosgene concentrations (see Attachment 3).

Attachment 1
Evaluation of Unexpected Test 41 Calibration Data

Analysis Reported April 2, 1999

Background:
The Test 41 calibration data (3/29/99) significantly deviated from past calibration data with respect to Miran absorbance units (AU) readings and drift between pre- and post-exposure calibrations. The readings for the 447 mg/m^3 calibration level increased from an average of 0.1557 AU to 0.1730 and 0.1924 AU (pre- and post-exposure calibrations, respectively). The drift increased from 3% to 5% for the same calibration level. Both these factors occurred to a lesser degree in the preceding exposure Test 39 (performed 3/8/99). An analysis was performed to determine what caused the unexpected data and whether the system can deliver the target concentrations in future exposures.

Analysis of Past Calibration Data:
There were16 phosgene tests at the 450 mg/m^3 level performed during Phase 2 prior to Tests 39 and 41. The calibration data from these tests was very consistent (Figure 1). Listed below is a statistical comparison of the previous 16 tests and Tests 39 and 41. Table 2 lists the calculated t-test values.

Second order polynomial regression for previous 18 tests:

$$Phosgene\ Conc.\left(\frac{mg}{m^3}\right) = -1719.7\,AU^2 + 3607.8\,AU - 72.247$$

$$R^2 = 0.9843$$

Table 1. Percent Deviation from Regression

	Previous 16 tests	Test 39	Test 41
Average (%)	0	-6	-17
Max (%)	3	-4	-9
Min (%)	-3	-9	-25
Std	1.3	2.1	7.2

Table 2. T Test Results ($t_{0.005}$ = 2.75 for df = 30)

Phosgene Calibration Conc. (mg/m^3)	t Value	
	Test 39	Test 41
388	-5.91	-11.27
447	-7.20	-12.02
506	-5.67	-10.86

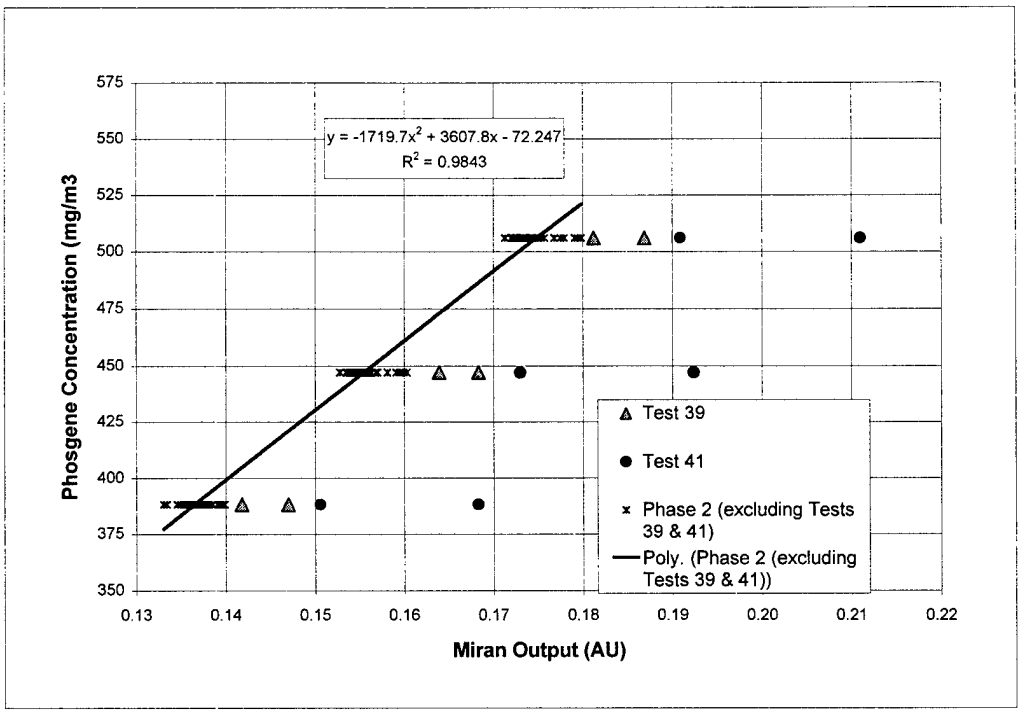

Figure 1. Phase 2 Calibration Data

As shown in Figure 2, the Tests 39 and 41 calibrations deviated significantly from the previous calibrations. Test 39 data are within the typical 10% acceptable limit, but the Test 41 data are over 20% from the expected values.

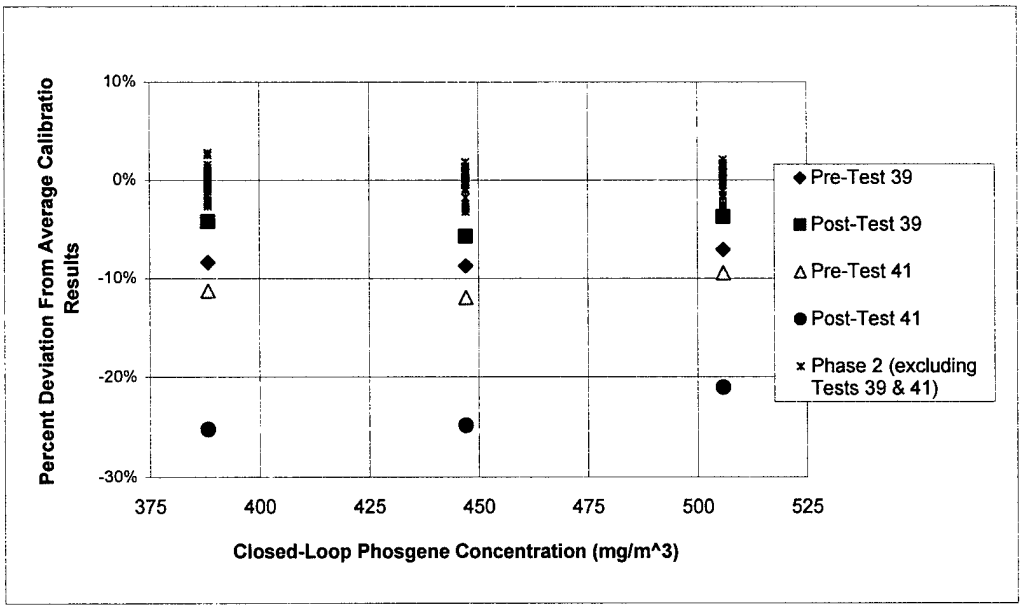

Figure 2. Percent Deviation from Average Calibration Data

Investigation of Potential Operator Error:
The Miran calibration procedures consist of injecting known volumes of a phosgene standard into a closed-loop system with a known internal volume. The only possibility for operator error would be the injection of the incorrect phosgene volumes. The technician has competently

carried out the calibration procedure over several months and there is no reason to believe this error occurred.

Investigation of Potential Miran Error:
The potential Miran malfunctions and performance degradations was discussed with Andy Szabo (Foxboro Technician, 508-549-3949). He stated that due to the way the Miran analyzed gases (monitoring infrared signal reduction), there is no logical reason for an increase AU for a given phosgene concentration.

System Check Results:
Three system calibrations were performed on 3/31/99 to determine if the problem was still present. Figure 3 compares the new calibration data with past Phase 2 and Test 41 calibration data. Tables 3 lists the percent deviation of the new calibration data from the averaged Phase 2 data while Table 4 lists the calculated t-test values for the same data.

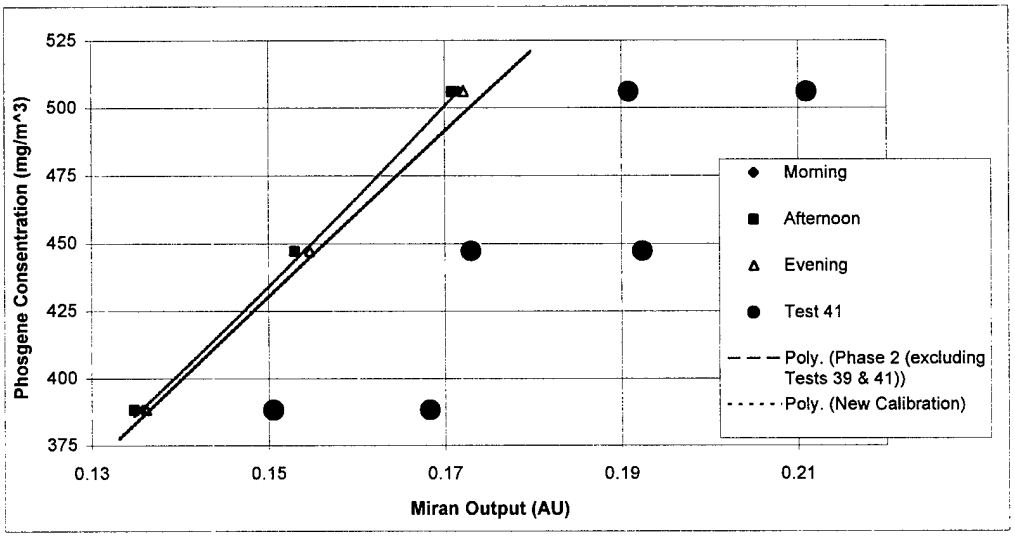

Table 3. Percent Deviation from Regression

	Previous 18 Tests	New Calibrations
Average (%)	0	1
Max (%)	3	2
Min (%)	-3	0
Std	1.3	0.7

Table 4. t-Test Results for New Calibration ($t_{0.005} = 2.75$ for df = 30)

Phosgene Calibration Conc. (mg/m^3)	t Value (df = 33)
388	1.11
447	1.48
506	2.16

Conclusions:
- The Test 41 calibration data significantly deviated from past calibration data.

- No cause for the unexpected Test 41 calibration data could be determined.
- New calibration data provide evidence that the system is functioning in a similar manner as previous tests.

Recommendations:

- Perform additional calibrations on 4/2/99 to verify that the system is ready for tests on 4/5/99.
- Perform two calibrations the morning of the 4/5/99 tests to verify that the system is functioning properly.
- Identify and establish post-calibration acceptance criteria in the testing room to provide easy indication that the system is functioning properly.

Table 5 lists 5% acceptance criteria, which is reasonable. The threshold values represent 5% deviation in calculated phosgene concentration using the Phase 2 regression equation listed above.

Table 5. Proposed Acceptance Criteria

Calibration Phosgene Conc. (mg/m^3)	Miran Output (AU)		
	Target	5% Lower Threshold	5% Higher Threshold
388	0.1365	0.1304	0.1427
447	0.1555	0.1482	0.1628
506	0.1748	0.1665	0.1833

Table 6 lists the calculated t-test values for the 5% acceptance Miran output values.

Table 6. Calculated t-Test Values for Acceptance Criteria Thresholds (df = 32)

Phosgene Calibration Conc. (mg/m^3)	5% Lower Threshold	5% Higher Threshold
388	5.19	-4.94
447	5.47	-5.11
506	4.87	-5.49

Attachment 2
Phosgene Decontamination Efficiency Evaluation

Analysis Reported June 22, 1999

An evaluation of a phosgene decontamination procedure was performed. Below is a description of the process.

Objective: To determine the phosgene decontamination efficiency of a gas wash bottle containing a 5% sodium hydroxide (NaOH) solution.

Test Setup: A 0.185 L/min 1% phosgene (balance nitrogen) flow was diluted with 15 L/min clean air for a resulting phosgene concentration of 500 mg/m^3, where the 1% phosgene concentration is 40,477 mg/m^3. The total flow was directed through a Miran 1B2 with the wavelength set to 11.98 μm and pathlength set to 0.75 m. Miran output (absorbance units or AU) was documented. A gas wash bottle containing a 3-inch depth of 5% NaOH solution was then put in line prior to the Miran and the same 500 mg/m^3 phosgene concentration was generated and the Miran output documented. The gas wash bottle was then removed from the system and the same 500 mg/m^3 phosgene concentration was generated again to document that the Miran output had not changed. The 1% phosgene flow was then reduce until the Miran output matched output noted when the gas wash bottle was in the system. This phosgene flow was used to calculate the phosgene concentration passed by the gas wash bottle.

Results:

Test Description	Clean Air Flow, L/min	1% Phosgene Flow, L/min	Miran Output, AU
Clean air background	15	off	0.0003
500 mg/m^3 baseline	15	0.185	0.1943
Clean air through gas wash battle	15	off	0.0022
Post gas wash bottle	15	0.185	0.0617
500 mg/m^3 baseline	15	0.185	0.1944
Matching of post gas wash bottle concentration	15	0.051	0.0620

Estimated post-gas wash bottle phosgene concentration = 138 mg/m^3

Conclusions:
Decontamination efficiency = 72%.

Attachment 3
Evaluation of Phosgene Degradation in Wetted Tygon® Tubing

Analysis Reported February 9, 1999

Background:
On 2/1/99 a concern was expressed that the water reactive phosgene exposure had to pass through a high humidity section of Tygon® tubing (1.4 cm I.D. and 12 cm in length) prior to being inhaled by the animal. This is part of the respirator to endotracheal tubing section (Figure 1). During most, if not all exposure tests, water droplets formed on the inner wall of this post-endotracheal tubing section due to animal exhalation.

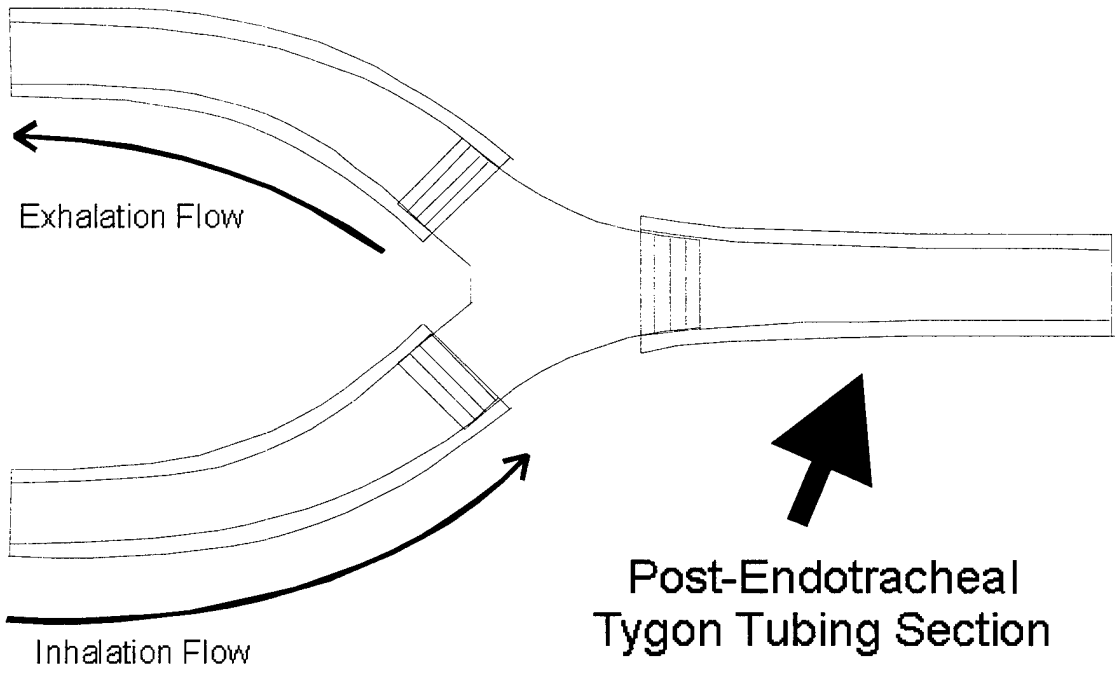

Figure 1. Tygon® Tubing Section Between Respirator and Endotracheal Tube.

If a significant percentage of the phosgene exposure has been degraded, the reported exposures may have been overstated. However, with all exposures using the same tubing section, one would expect any degradation to be similar for each exposure.

Objective:
To determine the degradation of phosgene concentration (%) due to transport through wetted Tygon® tubing sections.

Test Setup:
The existing phosgene exposure system was slightly modified to incorporate the test setup (Figure 2). Air and phosgene flows were maintained via mass flow controllers (MFC). The MFC were adjusted for a phosgene concentration of 450 mg/m^3 and their readings were identical for all tests (air 45.5% or ~15 L/min; 1% phosgene 26.2% or ~ 0.16 L/min). After the mixing T, a 3-way valve directed the flow either through a 1/4" Teflon® tube or a Tygon® tubing section (1.4 cm I.D. and either 12 or 152 cm in length). The flow was then directed into the Miran 1B2 (wavelength = 11.98 μm and pathlength = 0.75 m) for phosgene concentration measurement.

Miran output (absorbance units or AU) was documented. The phosgene concentrations were determined from a third-order regression of the Exposure Test 31 pre- and post-closed loop calibration data.

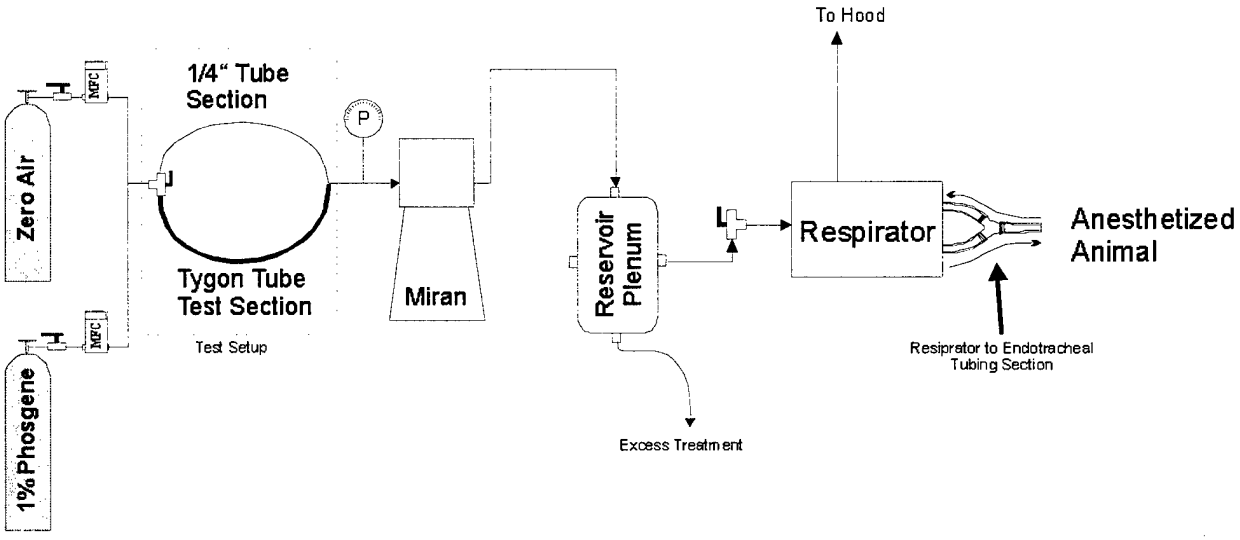

Figure 2. Test Setup Incorporated into Existing Phosgene Exposure System

The 12-cm long Tygon® tubing section was identical to that described in the Background section. The longer 152-cm Tygon® tubing section was included after no phosgene degradation was noted in the shorter tubing section.

Four tests were performed. In each test the flow was first directed through the 1/4" Teflon® tubing to establish the phosgene concentration. Then the flow was directed through the Tygon® tubing section (dry or wetted) to determine the change in phosgene concentration. Tests 1 and 2 evaluated the degradation in phosgene concentration due to the 12 cm long Tygon® tubing section (dry and wetted, respectively). Tests 3 and 4 evaluated the degradation in phosgene concentration due to the 152 cm long Tygon® tubing section (dry and wetted, respectively).

In Tests 2 and 4 the inside of the Tygon® tubing was wetted using a squirt bottle containing MREF tap water. In Test 2, the inside of the tube was misted several times to generate water droplets on internal walls. Excess water that had collected on the bottom of the tube was poured out. The degree of wetting was judged to be greater than that observed in the post-endotracheal tube Tygon® section during Tests 30 and 31 (concurrence by William Hart, MREF Technician). In Test 4, the inside of the tube was also misted several times to generate water droplets on internal walls. However, in this test the excess water that had collected on the bottom of the tube was not poured out. The tube was allowed to lay flat on the counter resulting in approximately 25% of the tube length to contain standing water.

Results:
Table 1 summarizes the test results. Percent phosgene concentration degradation was calculated with respect to the measured phosgene concentration that passed through the 1/4" Teflon® tubing section.

Table 1. Phosgene Concentration Degradation in Wetted Tygon® Tubing Results

Test	Description	Phosgene Concentration (mg/m^3)		Degradation (%)
		1/4" Teflon®	Tygon®	
1	Dry 12 cm Tygon®	451	451	negligible*
2	Wet 12 cm Tygon®	450	450	negligible
3	Dry 152 cm Tygon®	451	450	negligible
4	Wet 152 cm Tygon®	451	447	1

* Negligible - defined as less than 0.4% degradation.

Conclusion:
The wetted post-endotracheal Tygon® tubing section causes negligible degradation in phosgene concentration.

ATTACHMENT D

STATISTICAL REPORT FOR PHASE I

Battelle
. . . Putting Technology To Work

Project Number G1555-48ASTAT (3104)

Internal Distribution

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S:\Naga\Phase I Report_Converted-new\
Phase I Report Cover Memo-3.doc +
pmp Phase I report & tables-3.doc + pmp Phase I
Figures 1a-5b

Date June 19, 2000

To **Frances Reid**

From Nancy Niemuth

Subject **Statistical Report on Task 48, Phase I Experiments - Revision II**

Attached is the revised statistical report on Phase I experiments conducted under MREF Task 97-48. At your request, minor changes were made to this report to correct the animal groups shown in the table on page 1, the normal range for potassium on page 3, and the reference to Figure 4 on page 4. The text, tables, and figures prepared for this report will be provided electronically for use in your final report on Task 48.

The QA materials supporting this report were provided in our memo entitled "Study G1555-48A, MREF Task 97-48, Phase I QA Materials Supporting Phase I Statistical Report" on August 19, 1999. This memo will not be re-issued, as the data summary was not changed in this revised report.

As we noted previously, the report provides a descriptive analysis of Phase I model development experiments. The trends identified in this report may not be born out by statistical hypothesis tests, nor are they necessarily of clinical importance.

Please call me at 424-3231 if you have any questions or concerns regarding the attached report.

NAN:llj
Attachment

For Review and Approval

	Name	Internal	Date
Originator	Nancy Niemuth	N	6/19/00
Concurrence			
Approved	Bill Rosebrough	WRR	6/19/00

MREF TASK 97-48, PHASE 1:
STATISTICAL REPORT ON
MODEL DEVELOPMENT PHASE

INTRODUCTION

Phase I of Task 97-48 was conducted to develop an animal model that can be used for the assessment of treatment regimens for phosgene (CG) casualties. Seven animals were used to develop an experimental regimen for the 72-hour study. Eleven animals exposed to CG were used to select a dosing regimen for future efficacy studies. For the purpose of this report, four exposure groups were defined as follows.

Group	Animal ID	CG – Exposure (mg/m^3 min)	Survival (survived/n)
Anesthesia	98-105-3, 98-23-4, 98-24-4, 98-327-6, 98-345-5, 98-47-7[§], and 98-37-3	Air	NA
Control [*]	98-110-2, 98-236-6 and 98-23-4	Air	3/3
Low	98-51-3, and 98-60-2	2450 to 3300 CG	2/2
Medium	98-55-1, 98-33-3, 98-104-6, 98-18-5, 98-213-1 and 98-232-2	3700 to 4500 CG	3/6
High	98-50-7, 98-48-6, and 98-116-3, 98-45-3[†]	4900 to 5600 CG	0/3

§ No data collected. Not included in statistical analysis.

* For comparison to CG-exposed animals, one animal from anesthesia group and two air-exposed animals from Phase II experiments were selected. The techniques used on these animals were more similar to those used on CG-exposed animals than those of the remaining anesthesia animals from Phase I.

† Animal died before measurements could be taken. Not included in statistical analysis.

The clinical chemistry and hematology parameters evaluated in Phase I experiments were sodium (Na), potassium (K), chloride (Cl), blood urea nitrogen (BUN), glucose (Glu), arterial blood pH, partial pressure carbon dioxide (P_aCO_2), partial pressure of oxygen (P_aO_2), bicarbonate ion (HCO_3), total carbon dioxide (TCO_2), oxygen saturation (SO_2), base excess (BE), anion gap (An Gap), hemoglobin (Hb), and hematocrit (HCT). Respiratory endpoints evaluated in this experiment were expired CO_2, inspired O_2, oxygen saturation of capillary blood (SpO_2), pulse rate (PR), respiratory rate (RR), impedance of thoracic cavity, systolic blood pressure, diastolic blood pressure, and mean blood pressure. Heart rate (HR) measurements were not taken for animals in the anesthesia group. These parameters were measured immediately after exposure and thereafter approximately every hour for respiratory parameters and approximately every

and thereafter approximately every hour for respiratory parameters and approximately every four hours for clinical chemistry and hematology parameters, throughout the 72-hour study period.

For presentation purposes, time course designations were defined as follows. The measurement immediately after exposure was taken as time 0 for all parameters of interest. Thereafter, for respiratory parameters, time course periods were defined for every hour of the 72-hour study period. Each reading was assigned to the nearest time course period. For blood chemistry and hematology parameters, time course periods were defined at 1, 4, 8, 12 hours, etc. The 1 hour time course included any readings taken in the first 2 hours following the measurement at time 0. Later time courses included readings taken within ±2 hours of the labeled time. When multiple readings were taken within a time course period, the average was calculated.

Summary data tables display the number of observations (N), mean scores and associated standard errors at each time course designation for blood chemistry, hematology, and respiratory parameters. In addition, mean scores with standard error bars are displayed graphically. The time course variable was defined similarly for all parameters in the graphs.

This report provides a descriptive analysis of Phase I experiments. The trends identified in this report may not be born out by statistical hypothesis tests, nor are they necessarily of clinical importance. Normal ranges for several parameters were obtained from the study director, based on published data.

RESULTS

Anesthesia Group

Tables 1a, 1b, and 1c present summary statistics for clinical chemistry and hematology endpoints for the anesthesia group. As shown in Table 1a, standard errors for BUN and glucose were high, indicating that interanimal variability was large. From Table 1b, it is evident that P_aO_2 levels peaked at the end of the experiment and standard errors were relatively high. Figures 1a through 1f display this information graphically. From Figure 1a, sodium and chloride levels appear to have risen slightly and remained stable at the higher level, whereas potassium fluctuated within the normal range of 3.5 to 5.5 mmol/L, but did not exhibit any time trend. Both BUN and glucose levels rose and then fell (Figure 1b). BUN more than doubled during the first 32 hours, then returned to baseline in the next 32 hours. As seen in Figure 1c, P_aO_2 levels appear to have increased over time, with increasing variability over time. The pH levels rose somewhat during the first 4 hours of the experiment and remained stable at that higher level. P_aCO_2 declined slightly during the first 4 hours and then stabilized. TCO_2 and HCO_3 levels fluctuated together throughout the experiment, but no trends were observed (Figure 1d). SO_2 levels fluctuated during the first 24 hours, then rose for the remainder of the experiment. From Figure 1e, base excess levels exhibited relatively large variability and appeared to decline slightly over time. Hemoglobin and anion gap levels fluctuated during the 72-hour period. Hematocrit levels appeared to rise slightly around 48-hour, but otherwise fluctuated around the baseline level.

Tables 2a and 2b present the descriptive statistics for respiratory endpoints. Figures 2a through 2c display this information graphically. As indicated in Tables 2a and 2b, pulse rate, systolic blood pressure, diastolic blood pressure, and mean blood pressure exhibit great animal-to-animal variability. From Figure 2a, it appears that expired O_2 declined and inspired O_2 rose over time. Both systolic and diastolic blood pressure rose around 48 hours in the experiment (Figure 2b) and then returned to baseline levels. Mean BP (Figure 2c) followed the same trend. PR rose during the first 32 hours, then declined to levels below baseline. Respiratory rate was steady all through the experiment.

Phosgene(CG) Exposed Group

Tables 3a, 3b, and 3c present the descriptive statistics of clinical chemistry and hematology endpoints for control and CG-exposed animals. Figures 3a through 3o graphically

display this information. Sodium levels (Figure 3a) decreased until death in the high CG-exposed group and increased over the 72-hour study period in the other groups. Potassium (Figure 3b) and BUN (Figure 3d) for all groups increased over the first 8 hours, or until death, before returning to baseline levels in surviving animals. For all groups, chloride levels (Figure 3c) displayed an increasing trend over the 72-hour period. Glucose levels (Figure 3e) generally fluctuated within the normal range (82 to 150 mg/dL) throughout the 72-hour observation period for control, low, and medium CG-exposure groups. In the high exposure group, glucose levels declined toward 60 mg/dL within 4 to 8 hours, then increased before death. Baseline plasma pH values (Figure 3f) in all groups were above the reported normal mean of 7.391. The high CG-exposure group pH showed a steady decline until death. The medium CG-exposure group pH declined slightly over the first 12 hours and returned to baseline by 20 hours. The low CG-exposure group pH showed a similar trend, but remained within the normal range and resolved more rapidly, by 12 hours. P_aCO_2 (Figure 3g) increased until death in high CG-exposed animals, while in medium CG-exposed animals P_aCO_2 increased during the first 20 hours then returned to baseline for those that survived. P_aCO_2 remained at baseline levels for air control and low CG-exposed animals. P_aO_2 (Figure 3h) abruptly decreased until death in the high CG-exposure group. In the medium CG-exposure group, P_aO_2 levels declined over the first 12 hours and gradually increased to baseline. P_aO_2 levels in the control and low CG-exposure groups oscillated within the normal range (80-110 mm Hg) throughout the 72- hour study period. In the high CG-exposure group, bicarbonate ion (Figure 3i) and total CO_2 (Figure 3j) levels increased steadily until death, while other groups showed a steady decline over time. Oxygen saturation levels (Figure 3k) decreased abruptly until death in the high CG-exposure group and remained stable for all other groups. Base excess (Figure 3l) fluctuated until death in the high CG-exposure group and declined over the 72-hour period for other groups, although levels peaked in the low CG-exposure group at 4 hours. Anion gap (Figure 3m) for the high CG-exposure group declined at 4-hour, but returned to baseline by time of death. For all the other groups, anion levels oscillated throughout the observation period. Both hemoglobin (Figure 3n) and hematocrit (Figure 3o) levels declined initially and returned to baseline by 8 hours. Increased variability was observed after 36 hours in surviving animals.

Tables 4a and 4b present the descriptive statistics for respiratory parameters, while Figures 4a through 4i present this information graphically. As shown in Figure 4a, expired carbon dioxide levels peaked at 4 hours and gradually decreased over time in all study groups. Inspired oxygen levels (Figure 4b) were stable throughout the study period for all groups, except for a peak observed among low CG-exposed animals at 4 hours. Oxygen saturation levels (Figure 4c) fluctuated during study period for all groups. Steady decreases in heart rate

(Figure 4d) and pulse rate (Figure 4e) were observed for control animals. For other groups, heart rate and pulse rate increased during the first 12 hours and declined over the remainder of the 72-hour study period. Respiratory rates for control animals were lower than CG-exposed animals throughout the experiment. Systolic blood pressure, diastolic pressure, and mean blood pressure fluctuated together during the study period.

Impedance and Lung Wet:Dry Ratios

Summary statistics for wet to dry lung weight ratios are presented in Table 5. Mean wet to dry lung weight ratios in CG-exposed animals that survived were similar to those of control animals, indicating that PE had resolved. Mean wet to dry lung weight ratios in CG-exposed animals that died were greater than those of the control and CG-exposed animals that survived. The side of the lung that was up at death did not appear to have any effect on lung wet to dry ratios. Impedance cardiograph readings are plotted against time for all animals in Figure 5a for animals that survived the 72-hour study period and in Figure 5b for animals that died on study. Linear regression models were fitted to the impedance cardiograph readings for each animal, except for animal 98-51-3, whose readings displayed excessive curvature. Impedance cardiograph readings in surviving animals showed a linearly decreasing relationship with study time course. Animals that died before the 72-hour study period had very few observations and hence no inference could be drawn on those animals.

Table 1a. Descriptive Statistics for Sodium, Potassium, Chloride, Blood Urea Nitrogen (BUN), and Glucose by Study Time Course for Anesthesia Group.

Study Time Course	Sodium (mmol/L)		Potassium (mmol/L)		Chloride (mmol/L)		BUN (mg/dL)		Glucose (mg/dL)	
	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
0	5	136.80(0.97)	5	3.60(0.16)	5	105.40(2.04)	5	11.20(2.13)	5	69.60(9.24)
4	6	134.50(0.76)	6	4.47(0.42)	5	104.00(1.00)	5	15.00(2.39)	5	83.00(14.38)
8	6	134.50(0.56)	6	4.29(0.33)	6	105.00(1.79)	6	18.33(2.22)	6	99.42(5.87)
12	6	136.25(0.48)	6	3.96(0.13)	6	106.42(1.17)	6	19.50(2.65)	6	105.25(9.38)
16	5	136.50(0.89)	5	3.89(0.26)	5	106.30(1.04)	5	22.70(3.75)	5	105.30(12.42)
20	6	136.08(0.80)	6	4.17(0.43)	6	107.00(1.39)	6	23.58(3.99)	6	103.00(10.60)
24	6	138.00(1.32)	6	4.20(0.32)	6	107.67(0.80)	6	27.17(6.52)	6	112.50(15.46)
28	6	138.50(1.50)	6	4.52(0.67)	6	109.50(0.67)	6	27.33(8.78)	6	113.00(15.25)
32	4	140.00(0.82)	4	4.03(0.11)	4	109.75(1.80)	4	18.25(1.65)	4	100.50(5.58)
36	4	139.75(1.25)	4	3.95(0.13)	4	111.75(1.25)	4	16.25(1.38)	4	97.50(4.66)
40	4	140.50(1.26)	4	3.83(0.12)	4	112.00(1.41)	4	14.50(1.32)	4	91.25(6.54)
44	4	140.50(1.26)	4	3.95(0.14)	4	113.00(1.08)	4	12.25(0.75)	4	87.50(7.09)
48	3	141.67(0.67)	3	4.10(0.20)	3	112.33(1.20)	3	12.33(0.67)	3	82.33(5.46)
52	4	140.50(1.71)	4	3.98(0.10)	4	111.50(1.44)	4	11.50(0.65)	4	85.75(4.09)
56	3	139.50(1.80)	3	3.90(0.06)	3	110.83(2.09)	3	9.83(0.60)	3	88.33(4.70)
60	1	138.00(NA)	1	3.90(NA)	1	107.00(NA)	1	9.00(NA)	1	93.00(NA)
64	2	136.50(1.50)	2	3.70(0.30)	2	112.50(3.50)	2	7.50(0.50)	2	80.00(6.00)
68	2	137.50(0.50)	2	4.20(0.00)	2	109.50(1.50)	2	7.50(0.50)	2	79.50(5.50)

[1] SE=Standard Error

Table 1b. Descriptive Statistics for Arterial pH, Partial Pressure of CO_2 (P_aCO_2), Partial Pressure of O_2 (P_aO_2) Bicarbonate Ion (HCO_3), and Total CO_2 (TCO_2) by Study Time Course for Anesthesia Group.

Study Time Course	pH		PCO_2 (mm Hg)		PO_2 (mm Hg)		HCO_3 (mmol/L)		TCO_2 (mmol/L)	
	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
0	6	7.41(0.07)	6	39.50(3.58)	6	78.67(2.55)	6	25.00(2.25)	5	25.80(2.75)
4	6	7.50(0.02)	6	36.48(1.63)	6	65.17(3.70)	6	28.67(0.61)	6	29.67(0.61)
8	6	7.50(0.01)	6	34.49(2.64)	6	85.92(7.79)	6	27.08(1.87)	6	28.08(2.06)
12	6	7.49(0.01)	6	33.94(1.01)	6	77.17(6.16)	6	26.25(1.00)	6	27.33(1.05)
16	5	7.50(0.02)	5	34.35(2.71)	4	71.75(3.77)	5	26.50(1.43)	5	27.40(1.59)
20	6	7.50(0.01)	6	34.53(1.67)	6	69.67(6.56)	6	27.00(1.21)	6	28.17(1.25)
24	6	7.48(0.04)	6	34.30(1.66)	6	66.83(6.09)	6	25.50(1.34)	6	26.67(1.20)
28	6	7.48(0.05)	6	32.45(1.48)	6	75.67(6.75)	6	24.33(1.76)	6	25.17(1.74)
32	4	7.48(0.03)	4	34.35(1.75)	4	75.75(7.19)	4	25.50(1.04)	4	26.50(1.04)
36	4	7.50(0.01)	4	33.34(3.10)	4	70.50(8.63)	4	25.75(2.02)	4	26.75(2.02)
40	4	7.49(0.01)	4	32.28(2.66)	4	63.75(10.54)	4	24.50(2.02)	4	25.50(2.02)
44	4	7.48(0.02)	4	33.10(2.46)	4	81.50(14.52)	4	24.25(1.70)	4	24.75(1.49)
48	3	7.47(0.02)	3	34.80(0.42)	3	75.00(3.79)	3	25.67(1.20)	3	26.67(1.20)
52	4	7.48(0.01)	4	33.60(2.39)	4	86.25(13.61)	4	25.00(1.78)	4	26.00(1.78)
56	3	7.45(0.02)	3	35.22(3.04)	3	86.33(14.10)	3	24.50(2.02)	3	25.50(2.02)
60	1	7.49(NA)	1	35.60(NA)	1	82.00(NA)	1	27.00(NA)	1	28.00(NA)
64	2	7.48(0.01)	2	32.45(4.25)	2	96.50(9.50)	2	24.50(2.50)	2	25.00(3.00)
68	2	7.46(0.00)	2	34.35(4.45)	2	102.00(11.00)	2	24.50(3.50)	2	25.50(3.50)

[1] SE=Standard Error

Table 1c. Descriptive Statistics for Oxygen Saturation, Base Excess, Anion Gap Hemoglobin, and Hematocrit by Study Time Course for Anesthesia Group.

Study Time Course	Oxygen Saturation (%)		Base Excess (mmol/L)		Anion Gap (mmol/L)		Hemoglobin (g/dL)		Hematocrit (%)	
	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
0	6	94.50(1.93)	6	0.33(3.23)	5	9.40(0.98)	5	8.40(0.60)	5	24.40(1.29)
4	4	94.75(0.85)	6	5.33(0.56)	5	8.80(0.20)	5	9.20(0.86)	5	27.20(2.67)
8	6	96.58(0.93)	6	3.58(1.70)	6	8.58(0.86)	5	9.20(0.66)	6	23.33(3.08)
12	6	95.83(0.74)	6	2.83(0.97)	6	10.33(0.61)	5	9.20(0.56)	6	23.83(3.15)
16	5	96.40(0.98)	5	3.50(1.38)	5	10.20(0.86)	4	10.63(0.55)	5	26.20(4.28)
20	6	94.08(1.72)	6	3.92(1.39)	6	9.75(1.18)	5	9.90(0.81)	6	25.67(3.31)
24	6	93.00(2.13)	6	2.17(1.83)	6	11.17(0.70)	5	11.20(0.97)	6	28.50(4.33)
28	6	95.50(0.67)	6	0.50(2.57)	6	12.17(0.48)	5	10.80(0.58)	6	27.67(3.77)
32	3	95.00(2.00)	4	1.75(1.11)	4	11.25(0.48)	4	10.00(0.71)	4	30.00(2.12)
36	4	94.25(2.43)	4	2.88(2.07)	4	9.75(0.48)	4	10.50(1.04)	4	30.00(2.97)
40	3	94.33(2.19)	4	1.50(2.02)	4	9.75(0.75)	4	10.50(0.29)	4	30.75(0.48)
44	4	95.25(1.65)	4	0.75(1.65)	4	10.00(0.91)	4	8.75(0.63)	4	25.75(1.97)
48	3	96.00(0.58)	3	2.00(1.15)	3	10.33(1.86)	3	11.67(2.67)	3	34.00(7.51)
52	4	96.25(1.49)	4	1.25(1.93)	4	12.50(0.29)	4	9.75(1.31)	4	28.75(4.05)
56	3	95.83(2.46)	3	0.50(2.02)	3	10.83(0.60)	3	9.17(0.73)	3	27.00(2.31)
60	1	97.00(NA)	1	4.00(NA)	1	11.00(NA)	1	10.00(NA)	1	30.00(NA)
64	2	98.00(1.00)	2	0.50(2.50)	2	8.00(2.00)	2	9.50(3.50)	2	28.50(9.50)
68	2	98.50(0.50)	2	0.50(3.50)	2	11.50(0.50)	2	8.50(1.50)	2	26.00(4.00)

[1] SE=Standard Error

Table 2a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Pulse Rate, and Respiratory Rate by Study Time Course for Anesthesia Group.

Study Time Course	Expired CO_2 (mm Hg)		Inspired O_2 (%)		Oxygen Saturation (%)		Pulse Rate (Beats/Minute)		Respiratory Rate (Breaths/Minute)	
	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
0	3	41.67(6.36)	3	22.00(0.00)	2	97.50(1.50)	5	110.20(6.09)	4	31.25(9.12)
1	6	38.25(1.14)	6	22.00(0.00)	6	97.50(0.43)	6	117.00(5.19)	5	20.20(6.73)
2	6	38.42(1.13)	6	21.83(0.17)	6	97.00(0.68)	6	116.92(6.46)	5	19.40(5.94)
3	6	38.94(0.06)	6	29.28(7.08)	6	95.67(0.88)	6	114.39(5.24)	5	13.60(0.87)
4	6	39.00(0.58)	6	22.17(0.17)	6	94.17(1.22)	6	114.58(4.40)	5	13.80(0.73)
5	6	37.83(1.35)	6	22.17(0.17)	6	94.42(0.66)	6	125.17(12.43)	5	16.00(2.59)
6	6	38.58(1.58)	6	23.83(1.45)	6	96.50(1.31)	6	125.42(10.61)	5	14.20(0.97)
7	6	37.50(1.18)	6	27.08(3.40)	6	97.58(1.27)	6	114.75(6.98)	5	13.60(1.03)
8	6	37.92(0.90)	6	25.00(1.90)	6	97.75(1.15)	6	114.50(8.14)	5	13.20(0.73)
9	5	36.60(0.93)	5	25.40(1.89)	5	97.20(1.66)	5	121.00(12.32)	5	15.80(2.91)
10	4	36.00(0.91)	4	24.25(2.25)	4	99.25(0.48)	4	113.50(14.44)	4	13.50(0.87)
11	5	37.00(0.55)	5	25.40(2.09)	5	98.20(1.32)	5	126.40(9.79)	5	13.40(0.87)
12	5	36.40(0.68)	5	25.60(2.01)	5	97.80(1.46)	5	118.00(8.73)	5	13.20(0.73)
13	5	36.00(0.95)	5	27.20(2.15)	5	98.40(0.68)	5	119.40(8.07)	5	13.40(0.87)
14	5	36.40(0.68)	5	24.00(1.76)	5	96.80(1.46)	5	122.00(9.57)	5	13.40(0.87)
15	5	35.40(0.60)	5	23.80(1.80)	5	97.20(1.59)	5	123.00(14.18)	5	13.20(0.73)
16	5	37.20(1.16)	5	26.00(2.47)	5	99.20(0.37)	5	129.00(15.60)	5	12.80(0.97)
17	5	36.40(0.68)	5	25.80(2.33)	5	99.00(0.45)	5	121.80(15.00)	5	13.00(0.84)
18	5	35.60(0.51)	5	25.80(2.33)	5	97.20(1.62)	5	124.40(10.98)	5	13.00(0.84)
19	5	35.60(0.51)	5	30.00(3.89)	5	98.80(0.49)	5	124.00(11.90)	5	13.00(0.84)
20	5	35.00(0.89)	5	27.20(2.18)	5	98.60(0.87)	5	119.00(12.95)	5	13.00(0.84)
21	5	35.60(0.81)	5	26.80(1.98)	5	98.60(0.98)	5	124.60(13.43)	5	13.20(0.97)
22	5	36.00(0.89)	5	25.40(2.09)	5	96.80(1.07)	5	146.60(17.56)	5	13.00(0.89)
23	5	36.00(0.89)	5	25.40(2.09)	5	97.40(1.21)	5	144.00(21.80)	5	13.20(0.73)
24	4	37.50(2.22)	4	26.25(2.46)	4	97.75(1.44)	4	152.25(31.69)	4	12.50(0.87)
25	5	37.00(2.28)	5	25.40(2.09)	5	95.20(2.40)	5	137.40(20.73)	5	12.40(0.68)
26	5	37.00(2.28)	5	27.80(2.99)	5	94.20(2.27)	5	142.00(26.35)	5	13.00(0.84)
27	5	36.20(1.71)	5	27.60(2.42)	5	96.00(1.76)	5	146.60(28.07)	5	13.20(0.97)
28	5	36.00(2.02)	5	27.80(2.46)	5	97.40(0.68)	5	133.00(23.57)	5	12.80(0.97)
29	5	34.80(1.85)	5	27.20(2.65)	5	97.80(0.80)	5	127.00(18.88)	5	12.80(0.97)
30	5	37.40(1.54)	5	26.40(2.25)	5	97.80(0.86)	5	126.00(16.78)	5	14.20(2.35)
31	4	34.75(1.60)	4	25.75(2.78)	4	96.50(1.50)	4	107.75(11.32)	4	12.00(1.08)
32	4	34.75(1.89)	4	25.75(2.46)	4	96.25(1.55)	4	107.25(12.82)	4	12.00(1.08)
33	4	34.75(1.11)	4	25.75(2.46)	4	97.75(0.95)	4	106.00(8.28)	4	12.00(1.08)
34	4	34.75(1.70)	4	25.75(2.46)	4	98.00(0.41)	4	108.50(9.24)	4	12.00(1.08)
35	4	34.75(1.25)	4	25.75(2.46)	4	98.75(0.48)	4	106.25(8.07)	4	12.00(1.08)
36	4	34.75(1.44)	4	25.75(2.46)	4	96.75(1.60)	4	102.75(7.28)	4	12.00(1.08)
37	4	34.75(1.55)	4	25.75(2.46)	4	98.25(0.63)	4	100.25(8.56)	4	13.25(2.29)
38	4	33.50(0.65)	4	25.75(2.46)	4	95.75(1.44)	4	100.25(8.99)	4	12.00(1.08)
39	4	34.25(1.25)	4	27.75(1.93)	4	95.25(1.25)	4	99.25(4.27)	4	12.00(1.08)
40	4	33.50(1.19)	4	26.25(2.17)	4	94.25(2.17)	4	97.00(5.31)	4	12.00(1.08)
41	4	34.75(1.11)	4	28.25(2.10)	4	97.25(1.03)	4	98.00(4.06)	4	12.25(1.31)
42	4	35.75(1.11)	4	26.75(1.97)	4	96.00(2.42)	4	100.00(6.87)	4	11.25(0.48)
43	4	36.50(1.26)	4	26.25(2.17)	4	95.50(1.66)	4	98.00(3.19)	4	11.25(0.48)
44	4	36.00(1.22)	4	27.75(1.93)	4	98.00(0.71)	4	99.25(6.30)	4	11.25(0.48)

Table 2a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Pulse Rate, and Respiratory Rate by Study Time Course for Anesthesia Group (Continued)

Study Time Course	Expired CO_2 (mm Hg)		Inspired O_2 (%)		Oxygen Saturation (%)		Pulse Rate (Beats/Minute)		Respiratory Rate (Breaths/Minute)	
	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
45	4	34.75(1.11)	4	29.50(0.50)	4	99.00(0.58)	4	97.00(11.56)	4	11.75(1.18)
46	4	35.00(0.71)	4	30.00(0.71)	4	98.50(0.65)	4	96.50(8.43)	4	11.25(0.48)
47	4	36.00(1.63)	4	29.75(0.25)	4	98.75(0.48)	4	91.25(5.15)	4	12.50(1.55)
48	3	34.67(0.88)	3	30.00(0.00)	3	99.00(0.58)	3	91.33(3.28)	3	11.33(0.67)
49	4	32.50(1.85)	4	29.00(1.00)	4	97.88(0.13)	4	99.13(6.34)	4	15.00(4.02)
50	4	35.75(0.48)	4	30.00(0.41)	4	94.75(3.94)	4	103.75(7.94)	4	14.00(3.37)
51	4	33.00(1.58)	4	28.00(2.35)	4	95.50(3.20)	4	98.75(10.33)	4	11.25(0.48)
52	4	32.75(2.14)	4	29.00(2.92)	4	93.50(3.77)	4	100.75(11.26)	4	13.25(2.29)
53	4	32.75(2.39)	4	30.25(1.44)	3	99.00(0.00)	4	112.25(17.38)	4	12.50(1.55)
54	4	33.50(2.40)	4	31.00(1.73)	4	99.25(0.48)	4	102.25(11.03)	4	11.25(0.48)
55	4	34.25(2.32)	4	31.50(0.96)	4	93.25(4.31)	4	103.25(6.25)	4	11.25(0.48)
56	4	34.63(2.25)	4	31.13(1.48)	4	99.25(0.48)	4	111.50(10.43)	4	14.50(3.52)
57	4	36.00(2.27)	4	31.25(1.60)	4	98.25(1.11)	4	100.75(5.02)	4	11.25(0.48)
58	4	33.75(1.03)	4	33.50(2.06)	4	98.75(0.95)	4	91.75(8.84)	4	13.25(2.29)
59	4	33.50(1.50)	4	32.75(1.93)	4	96.50(2.02)	4	95.50(8.11)	4	11.25(0.48)
60	4	34.25(1.65)	4	33.50(2.18)	4	97.25(1.55)	4	93.25(4.15)	4	12.50(1.55)
61	4	33.25(1.11)	4	33.75(2.25)	4	98.50(1.19)	4	90.25(5.95)	4	11.25(0.48)
62	4	34.75(1.75)	4	32.25(2.81)	4	96.75(2.14)	4	92.25(5.48)	4	14.00(3.03)
63	4	33.50(1.32)	4	32.00(1.41)	4	96.75(1.60)	4	91.50(7.15)	4	11.25(0.48)
64	4	33.50(2.40)	4	33.50(2.06)	4	98.00(1.22)	4	91.00(5.12)	4	11.25(0.48)
65	4	33.50(1.44)	4	33.75(2.25)	4	98.50(0.96)	4	93.50(6.51)	4	11.25(0.48)
66	4	36.25(1.93)	4	33.00(2.04)	4	98.75(0.95)	4	86.25(7.20)	4	10.75(0.48)
67	4	32.75(1.49)	4	32.50(1.76)	4	98.00(1.35)	4	86.25(9.32)	4	10.75(0.48)
68	4	34.00(2.80)	4	31.75(1.55)	4	96.25(2.25)	4	91.25(6.99)	4	12.50(2.18)
69	4	32.50(2.50)	4	30.75(1.80)	4	97.25(1.18)	4	91.50(8.39)	4	15.00(4.67)
70	2	35.50(1.50)	2	30.00(0.00)	2	93.50(2.50)	2	85.50(3.50)	2	10.50(0.50)

[1] SE=Standard Error

Table 2b. Descriptive Statistics for Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Study Time Course for Anesthesia Group.

Study Time Course	Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
0	0	NA (NA)	3	108.33(6.17)	3	67.00(3.21)	3	85.00(4.36)
1	2	18.43(0.32)	5	109.40(5.99)	5	64.20(4.92)	5	82.00(5.55)
2	3	18.80(0.95)	5	108.20(7.98)	5	62.60(6.73)	5	81.20(8.25)
3	3	19.43(1.23)	5	109.40(9.74)	5	66.60(6.70)	5	82.60(7.49)
4	3	18.93(0.58)	5	107.80(7.20)	5	57.20(12.03)	5	80.40(6.00)
5	3	18.20(0.85)	5	106.80(10.13)	5	71.80(10.27)	5	85.00(9.94)
6	3	18.30(0.82)	5	104.60(10.39)	5	66.40(9.01)	5	79.60(9.44)
7	3	18.47(0.75)	5	106.20(9.30)	5	61.60(6.64)	5	77.40(7.76)
8	3	18.20(0.96)	5	107.60(9.82)	5	62.00(6.27)	5	78.00(7.92)
9	3	18.40(1.14)	5	107.60(10.20)	5	65.00(8.56)	5	82.20(9.69)
10	2	17.80(2.10)	4	108.00(14.60)	4	64.25(11.32)	4	78.75(12.63)
11	3	18.38(0.91)	5	116.00(8.48)	5	75.50(7.75)	5	91.20(8.58)
12	3	18.77(0.58)	5	109.00(7.60)	5	63.60(4.79)	5	80.20(6.02)
13	3	18.13(0.52)	5	112.00(4.88)	5	67.80(4.65)	5	83.60(4.34)
14	3	18.43(0.72)	5	113.00(8.67)	5	69.80(7.60)	5	85.00(7.41)
15	3	18.63(0.79)	5	102.80(4.58)	5	67.80(5.41)	5	80.00(3.86)
16	3	18.60(0.68)	5	104.60(9.51)	5	62.60(6.46)	5	78.20(7.51)
17	3	18.87(0.78)	5	101.20(10.49)	5	60.40(9.27)	5	84.20(7.43)
18	3	18.83(0.92)	5	104.40(10.91)	5	61.80(8.24)	5	78.40(8.61)
19	3	18.20(0.50)	5	100.80(4.53)	5	58.80(4.32)	5	73.00(4.29)
20	3	18.43(0.84)	5	102.80(4.99)	5	59.60(3.78)	5	74.60(4.34)
21	3	18.27(1.00)	5	110.40(5.48)	5	68.60(6.20)	5	83.00(6.14)
22	3	18.07(1.03)	5	117.20(4.77)	5	73.40(6.74)	5	88.20(4.91)
23	3	18.03(0.90)	5	105.80(6.26)	5	67.00(6.06)	5	81.00(5.36)
24	2	18.60(0.60)	3	103.33(5.70)	3	61.67(3.76)	3	76.33(3.84)
25	3	18.40(0.50)	4	109.75(1.49)	4	65.25(3.04)	4	76.25(5.72)
26	3	18.67(0.73)	5	103.00(4.83)	5	63.40(5.18)	5	78.00(5.04)
27	3	18.33(0.75)	5	106.20(2.31)	5	64.80(2.35)	5	80.40(1.50)
28	3	18.23(0.90)	5	96.60(7.88)	5	56.80(4.42)	5	70.20(5.03)
29	3	18.37(0.81)	5	100.20(7.31)	5	54.20(6.09)	5	70.80(6.64)
30	3	18.20(0.55)	5	99.40(10.83)	5	52.00(7.79)	5	69.60(8.77)
31	3	17.37(0.96)	4	107.75(4.31)	4	60.25(4.66)	4	76.75(4.17)
32	3	17.20(0.93)	4	102.00(7.13)	4	59.00(7.06)	4	73.75(7.75)
33	3	17.20(0.87)	4	112.00(4.43)	4	62.75(3.73)	4	80.75(3.28)
34	3	17.60(0.75)	4	107.50(11.84)	4	62.25(6.75)	4	79.50(8.29)
35	3	17.80(0.76)	3	112.67(6.69)	3	65.00(3.61)	3	83.00(4.51)
36	3	17.37(0.98)	4	98.00(9.60)	4	62.00(3.81)	4	75.75(4.50)
37	3	17.43(0.96)	4	104.25(4.21)	4	63.75(6.09)	4	79.00(5.05)
38	3	17.67(0.85)	4	111.50(7.01)	4	69.25(6.34)	4	85.75(6.28)
39	3	17.53(0.88)	4	109.75(4.70)	4	73.50(7.33)	4	86.75(4.82)
40	3	17.33(0.52)	4	111.00(4.08)	4	71.00(6.79)	4	86.50(5.39)
41	3	17.17(0.72)	4	110.75(2.59)	4	68.75(2.25)	4	86.25(2.21)
42	3	17.57(0.65)	4	112.25(4.27)	4	73.00(6.12)	4	89.00(4.49)
43	3	17.37(0.78)	4	114.50(6.93)	4	77.50(7.60)	4	90.50(6.38)

Table 2b. Descriptive Statistics for Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Study Time Course for Anesthesia Group (Continued)

Study Time Course	Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Pressure (mm Hg)		Mean BP (mm Hg)	
	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
44	3	17.33(0.85)	4	116.75(5.53)	4	79.50(6.51)	4	93.50(6.22)
45	3	17.27(0.90)	4	107.25(6.65)	4	66.25(5.88)	4	82.50(5.11)
46	3	17.40(0.72)	4	115.00(2.97)	4	68.00(3.03)	4	86.00(1.47)
47	3	17.57(0.74)	4	111.00(1.08)	4	61.75(6.66)	4	79.00(4.69)
48	2	17.30(1.90)	3	106.33(7.33)	3	69.67(4.63)	3	82.67(2.73)
49	3	17.18(1.14)	4	120.13(9.27)	4	77.25(3.71)	4	92.88(3.96)
50	3	17.17(1.48)	4	145.50(12.26)	4	102.25(20.64)	4	98.25(3.42)
51	3	18.40(1.10)	4	140.50(15.73)	4	96.00(23.98)	4	112.75(20.30)
52	3	17.47(0.99)	4	131.75(16.01)	4	97.25(20.35)	4	110.50(17.58)
53	3	17.70(0.66)	4	124.75(18.27)	4	89.00(19.87)	4	102.75(18.06)
54	3	17.57(0.88)	4	130.50(8.70)	4	91.00(16.31)	4	106.25(12.26)
55	3	17.47(1.08)	4	126.25(7.98)	4	90.50(16.26)	4	105.00(11.81)
56	3	17.12(1.31)	3	118.00(5.77)	3	84.83(10.46)	3	94.17(8.67)
57	3	17.10(0.75)	3	107.00(10.97)	3	69.00(5.20)	3	82.67(5.67)
58	3	17.57(0.47)	3	111.00(3.79)	3	62.00(2.31)	3	80.00(3.00)
59	3	17.83(0.41)	3	111.67(6.94)	3	66.33(8.25)	3	84.00(7.81)
60	3	18.30(0.74)	3	109.33(6.39)	3	67.00(7.37)	3	83.00(6.66)
61	3	18.40(0.81)	3	105.33(5.93)	3	65.33(1.86)	3	80.33(1.20)
62	3	17.77(0.48)	3	107.00(7.57)	3	65.00(8.39)	3	81.33(7.13)
63	3	17.80(0.61)	3	106.00(7.94)	3	66.67(0.88)	3	81.67(2.96)
64	3	17.80(1.10)	3	100.00(8.50)	3	60.00(0.58)	3	72.67(2.19)
65	3	18.00(0.81)	3	105.67(4.70)	3	65.33(4.91)	3	81.00(2.65)
66	3	18.73(1.04)	3	97.33(5.24)	3	60.00(5.69)	3	73.67(0.88)
67	3	18.70(1.13)	3	99.67(6.49)	3	63.67(1.76)	3	77.00(2.65)
68	3	18.30(0.87)	3	102.33(6.74)	3	67.33(11.20)	3	82.67(10.17)
69	3	18.17(0.71)	3	104.67(5.78)	3	76.67(8.57)	3	86.67(4.70)
70	2	18.80(1.00)	1	93.00(NA)	1	57.00(NA)	1	73.00(NA)

[1] SE=Standard Error

Table 3a. Descriptive Statistics for Sodium, Potassium, Chloride, Blood Urea Nitrogen (BUN), and Glucose by Study Time Course in Air Control and CG-Exposed Groups.

Group	Study Time Course	Sodium (mmol/L)		Potassium (mmol/L)		Chloride (mmol/L)		BUN (mg/dL)		Glucose (mg/dL)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
Control	0	3	136.67(1.20)	3	3.80(0.26)	3	105.00(2.08)	3	11.67(0.88)	3	94.33(4.81)
	1	1	135.00(NA)	1	3.40(NA)	1	106.00(NA)	1	15.00(NA)	1	91.00(NA)
	4	3	135.33(1.86)	3	4.57(0.37)	3	104.17(1.64)	3	14.50(1.89)	3	106.83(6.22)
	8	3	136.33(1.76)	3	4.23(0.48)	3	104.67(0.88)	3	18.67(2.67)	3	116.00(7.00)
	12	3	138.17(1.42)	3	3.62(0.06)	3	107.17(0.44)	3	18.50(3.50)	3	104.17(4.42)
	16	2	139.00(2.00)	2	3.80(0.10)	2	108.50(0.50)	2	19.00(7.00)	2	105.50(1.50)
	20	3	138.67(1.67)	3	3.67(0.07)	3	110.33(1.67)	3	18.67(3.38)	3	98.00(2.00)
	24	3	139.67(0.67)	3	3.73(0.07)	3	111.00(1.15)	3	18.00(3.51)	3	92.33(3.53)
	28	3	139.33(0.67)	3	3.60(0.10)	3	112.00(2.65)	3	15.67(3.84)	3	88.00(4.73)
	32	3	140.33(0.88)	3	4.10(0.10)	3	109.33(0.33)	3	14.67(2.85)	3	95.67(2.33)
	36	2	141.50(1.50)	2	3.90(0.00)	2	112.00(0.00)	2	11.50(3.50)	2	89.50(3.50)
	40	3	140.33(1.76)	3	4.13(0.09)	3	111.00(1.00)	3	12.33(2.19)	3	91.33(4.41)
	44	3	140.33(1.76)	3	3.97(0.15)	3	112.00(1.53)	3	11.67(2.33)	3	84.67(5.24)
	48	3	140.33(0.67)	3	3.77(0.29)	3	116.67(3.53)	3	11.67(2.40)	3	72.33(6.17)
	52	3	139.67(1.20)	3	4.07(0.13)	3	111.33(1.76)	3	12.33(2.03)	3	84.00(4.73)
	56	3	140.50(1.76)	3	3.87(0.03)	3	110.17(0.83)	3	12.50(2.75)	3	89.67(2.19)
	60	3	140.00(1.53)	3	3.80(0.10)	3	110.00(1.73)	3	12.67(2.73)	3	92.00(2.65)
	64	3	140.00(1.53)	3	3.83(0.17)	3	112.00(1.73)	3	10.67(1.45)	3	85.33(0.67)
	68	3	139.00(1.53)	3	3.83(0.20)	3	113.33(2.73)	3	10.00(1.00)	3	78.00(5.13)
	72	2	140.50(1.50)	2	3.55(0.15)	2	116.50(1.50)	2	10.00(1.00)	2	78.00(2.00)
Low	0	2	136.00(4.00)	2	3.75(0.15)	2	101.00(3.00)	2	7.50(1.50)	2	78.50(18.50)
	1	2	136.50(4.50)	2	3.65(0.05)	2	103.00(4.00)	2	8.00(1.00)	2	81.50(16.50)
	4	2	134.50(3.50)	2	4.45(0.15)	2	98.50(4.50)	2	9.50(0.50)	2	96.50(15.50)
	8	2	134.00(2.00)	2	5.20(0.70)	2	100.50(1.50)	2	15.00(1.00)	2	135.50(15.50)
	12	2	135.50(4.50)	2	3.55(0.15)	2	103.00(2.00)	2	16.50(4.50)	2	105.50(3.50)
	16	2	136.50(4.50)	2	3.50(0.00)	2	105.00(0.00)	2	14.00(4.00)	2	103.50(8.50)
	20	2	138.50(4.50)	2	3.50(0.30)	2	105.50(2.50)	2	12.50(2.50)	2	96.00(5.00)
	24	2	137.00(3.00)	2	3.90(0.10)	2	105.50(3.50)	2	12.00(2.00)	2	94.50(10.50)
	28	2	137.50(3.50)	2	3.95(0.05)	2	104.50(2.50)	2	12.50(2.50)	2	99.00(9.00)
	32	2	137.00(3.00)	2	3.75(0.15)	2	106.50(3.50)	2	12.50(1.50)	2	121.00(32.00)
	36	2	138.00(3.00)	2	3.70(0.20)	2	105.25(2.75)	2	11.25(2.25)	2	117.25(6.75)
	40	2	138.00(3.00)	2	3.85(0.15)	2	107.50(2.50)	2	9.00(2.00)	2	101.50(1.50)
	44	2	138.50(2.50)	2	3.95(0.25)	2	107.00(3.00)	2	8.00(1.00)	2	97.00(1.00)
	48	2	136.50(3.50)	2	4.25(0.35)	2	110.50(0.50)	2	14.50(5.50)	2	91.50(3.50)
	52	2	136.00(3.00)	2	4.40(1.00)	2	109.00(4.00)	2	20.50(12.50)	2	148.00(44.00)
	56	2	136.75(2.75)	2	4.48(0.53)	2	109.00(0.00)	2	19.75(12.25)	2	112.25(8.75)
	60	2	138.50(0.50)	2	3.95(0.15)	2	106.50(1.50)	2	16.50(9.50)	2	105.00(8.00)
	64	2	139.00(1.00)	2	3.50(0.00)	2	110.00(2.00)	2	14.00(7.00)	2	94.00(9.00)
	68	2	144.50(4.50)	2	3.45(0.45)	2	114.50(5.50)	2	13.00(5.00)	2	69.50(13.50)
	72	2	138.00(0.00)	2	4.45(0.05)	2	109.00(0.00)	2	21.50(13.50)	2	94.50(11.50)

Table 3a. Descriptive Statistics for Sodium, Potassium, Chloride, Blood Urea Nitrogen (BUN), and Glucose by Study Time Course in Air Control and CG-Exposed Groups (Continued)

Group	Study Time Course	Sodium (mmol/L)		Potassium (mmol/L)		Chloride (mmol/L)		BUN (mg/dL)		Glucose (mg/dL)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
Medium	0	6	139.17(0.48)	6	3.65(0.20)	6	104.17(0.79)	6	9.50(0.62)	6	93.83(15.85)
	1	6	138.17(0.65)	6	3.37(0.15)	6	107.67(1.87)	6	10.00(0.77)	6	94.67(12.63)
	4	6	136.83(0.83)	6	4.15(0.18)	6	107.00(2.03)	6	13.83(1.08)	6	112.83(12.26)
	8	6	138.92(1.45)	6	4.19(0.45)	6	106.83(1.30)	6	17.08(1.29)	6	120.50(7.52)
	12	4	138.25(0.75)	4	3.90(0.32)	4	106.63(1.72)	4	17.50(1.85)	4	124.13(7.39)
	16	4	138.75(1.44)	4	3.38(0.19)	4	110.50(2.33)	4	14.75(2.06)	4	107.50(5.39)
	20	4	140.50(0.87)	4	3.45(0.16)	4	108.00(0.71)	4	13.50(1.66)	4	105.25(5.45)
	24	3	139.67(1.45)	3	3.80(0.06)	2	107.00(1.00)	3	12.67(2.33)	3	105.67(3.93)
	28	3	141.00(1.15)	3	4.03(0.26)	3	109.67(0.67)	3	12.33(1.76)	3	95.33(6.12)
	32	3	140.67(0.33)	3	4.40(0.12)	3	108.33(1.33)	3	13.67(1.33)	3	100.67(6.01)
	36	3	143.00(3.46)	3	4.10(0.12)	3	111.67(1.76)	3	14.33(1.45)	3	96.67(8.01)
	40	2	139.50(0.50)	2	4.30(0.10)	2	109.00(1.00)	2	15.50(2.50)	2	98.50(14.50)
	44	2	138.50(0.50)	2	4.15(0.55)	2	115.00(5.00)	2	14.00(3.00)	2	91.50(1.50)
	48	2	141.00(2.00)	2	3.70(0.30)	2	114.00(1.00)	2	13.50(2.50)	2	91.00(3.00)
	52	1	137.00(NA)	1	3.50(NA)	1	125.00(NA)	1	10.00(NA)	1	101.00(NA)
	56	2	143.00(3.00)	2	4.25(0.05)	2	106.50(3.50)	2	12.50(1.50)	2	102.00(8.00)
	60	1	142.00(NA)	1	4.10(NA)	1	106.00(NA)	1	10.00(NA)	1	109.00(NA)
	64	2	143.00(4.00)	2	4.30(0.50)	2	108.00(2.00)	2	10.50(0.50)	2	95.00(5.00)
	68	0	NA (NA)	0	NA (NA)	0	NA (NA)	0	NA (NA)	1	83.00(NA)
	72	3	140.00(1.00)	3	3.73(0.35)	3	115.00(2.08)	3	10.00(0.58)	3	81.67(6.57)
High	0	3	139.00(0.58)	3	3.53(0.09)	3	104.00(0.58)	3	8.67(1.33)	3	78.00(16.26)
	1	3	137.33(0.88)	3	3.13(0.28)	3	109.33(1.45)	3	9.00(1.73)	3	57.67(4.63)
	4	3	137.67(0.88)	3	4.17(0.07)	3	103.00(1.53)	3	13.00(1.00)	3	62.67(2.96)
	8	2	136.25(0.25)	2	5.30(0.60)	2	104.00(2.00)	2	19.75(1.25)	2	105.75(6.75)
Death		5	138.40(1.08)	5	5.02(0.65)	5	107.60(1.47)	5	18.00(1.38)	5	109.60(9.42)

[1] SE=Standard Error

Table 3b. Descriptive Statistics for Arterial pH, Partial Pressure of CO_2 (P_aCO_2), Partial Pressure of O_2 (P_aO_2) Bicarbonate Ion (HCO_3), and Total CO_2 (TCO_2) by Study Time Course in Air Control and CG-Exposed Groups.

Group	Study Time Course	pH		P_aCO_2 (mm Hg)		P_aO_2 (mm Hg)		HCO_3 (mmol/L)		TCO_2 (mmol/L)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
Control	0	3	7.51(0.01)	3	36.70(2.44)	3	93.00(21.13)	3	29.00(2.52)	3	30.00(2.52)
	1	1	7.55(NA)	1	30.20(NA)	1	153.00(NA)	1	26.00(NA)	1	27.00(NA)
	4	3	7.47(0.02)	3	37.85(2.43)	3	97.33(23.50)	3	27.67(0.33)	3	28.67(0.33)
	8	3	7.47(0.02)	3	38.60(2.10)	3	99.67(4.91)	3	28.33(2.67)	3	30.00(2.52)
	12	3	7.48(0.02)	3	37.17(1.70)	3	102.33(6.49)	3	27.33(0.88)	3	28.67(1.20)
	16	2	7.48(0.00)	2	37.65(0.15)	2	104.00(7.00)	2	28.00(0.00)	2	29.50(0.50)
	20	3	7.49(0.01)	3	33.23(1.13)	3	104.00(11.36)	3	25.33(1.45)	3	26.33(1.45)
	24	3	7.49(0.01)	3	33.13(1.39)	3	104.00(8.72)	3	25.00(1.00)	3	26.00(1.00)
	28	3	7.48(0.01)	3	32.40(1.80)	3	94.00(4.58)	3	24.00(1.73)	3	25.00(1.73)
	32	3	7.48(0.01)	3	35.80(1.17)	3	89.00(1.53)	3	26.67(0.88)	3	27.67(0.88)
	36	2	7.51(0.01)	2	34.90(1.80)	2	82.00(2.00)	2	27.50(0.50)	2	28.50(0.50)
	40	3	7.50(0.01)	3	32.57(2.75)	3	95.67(12.44)	3	25.33(2.19)	3	26.33(2.19)
	44	3	7.49(0.03)	3	31.23(1.81)	3	92.00(9.07)	3	23.67(0.33)	3	24.67(0.33)
	48	3	7.49(0.01)	3	28.30(3.56)	3	94.67(10.35)	3	21.67(3.18)	3	22.33(3.38)
	52	3	7.48(0.02)	3	32.63(2.55)	3	84.00(3.51)	3	24.33(1.33)	3	25.00(1.53)
	56	3	7.50(0.03)	3	32.98(3.64)	3	97.33(4.37)	3	25.50(1.61)	3	26.50(1.61)
	60	3	7.49(0.02)	3	31.13(2.72)	3	95.33(8.11)	3	23.67(1.67)	3	24.67(1.67)
	64	3	7.50(0.02)	3	30.47(3.13)	3	91.33(3.84)	3	23.33(1.86)	3	24.33(1.86)
	68	3	7.49(0.02)	3	29.13(4.91)	3	101.67(6.36)	3	22.00(3.00)	3	22.67(3.18)
	72	2	7.51(0.02)	2	23.65(0.45)	2	113.00(2.00)	2	18.50(0.50)	2	19.50(0.50)
Low	0	2	7.53(0.02)	2	37.10(1.80)	2	96.00(8.00)	2	31.00(0.00)	2	32.00(0.00)
	1	2	7.45(0.00)	2	42.05(0.25)	2	78.00(4.00)	2	29.50(0.50)	2	30.50(0.50)
	4	2	7.50(0.02)	2	43.35(1.25)	2	100.00(5.00)	2	33.50(2.50)	2	35.00(2.00)
	8	2	7.51(0.02)	2	37.80(0.10)	2	117.00(20.00)	2	30.50(1.50)	2	31.50(1.50)
	12	2	7.53(0.00)	2	34.60(0.00)	2	74.50(0.50)	2	29.00(0.00)	2	30.00(0.00)
	16	2	7.53(0.00)	2	31.90(2.60)	2	78.00(0.00)	2	27.00(2.00)	2	27.50(2.50)
	20	2	7.53(0.01)	2	32.25(1.25)	2	77.00(4.00)	2	27.50(0.50)	2	28.50(0.50)
	24	2	7.51(0.05)	2	35.85(3.75)	2	64.50(11.50)	2	28.00(0.00)	2	29.00(0.00)
	28	2	7.53(0.01)	2	34.05(0.55)	2	82.00(6.00)	2	28.50(1.50)	2	29.50(1.50)
	32	2	7.54(0.05)	2	29.40(2.60)	2	82.50(12.50)	2	25.50(0.50)	2	26.50(0.50)
	36	2	7.48(0.00)	2	35.18(0.88)	2	78.75(4.75)	2	26.25(0.75)	2	27.25(0.75)
	40	2	7.52(0.00)	2	31.40(1.10)	2	82.50(14.50)	2	26.00(1.00)	2	27.00(1.00)
	44	2	7.46(0.00)	2	36.65(2.15)	2	76.00(2.00)	2	26.50(1.50)	2	27.50(1.50)
	48	2	7.45(0.01)	2	34.10(1.10)	2	69.50(17.50)	2	24.00(1.00)	2	25.00(1.00)
	52	2	7.38(0.07)	2	36.35(3.75)	2	95.00(2.00)	2	21.50(1.50)	2	22.50(0.50)
	56	2	7.45(0.01)	2	34.13(1.17)	2	95.50(5.50)	2	23.75(0.25)	2	24.75(0.25)
	60	2	7.47(0.01)	2	35.85(0.45)	2	91.50(8.50)	2	26.00(0.00)	2	27.00(0.00)
	64	2	7.46(0.05)	2	36.65(2.75)	2	87.50(11.50)	2	26.00(1.00)	2	27.00(1.00)
	68	2	7.43(0.02)	2	27.85(9.85)	2	71.50(4.50)	2	19.00(7.00)	2	19.50(7.50)
	72	2	7.42(0.01)	2	31.10(4.30)	2	104.50(22.50)	2	20.00(2.00)	2	21.00(2.00)

Table 3b. Descriptive Statistics for Arterial pH, Partial Pressure of CO_2 (P_aCO_2), Partial Pressure of O_2 (P_aO_2) Bicarbonate Ion (HCO_3), and Total CO_2 (TCO_2) by Study Time Course in Air Control and CG-Exposed Groups (Continued)

Group	Study Time Course	pH		P_aCO_2 (mm Hg)		P_aO_2 (mm Hg)		HCO_3 (mmol/L)		TCO_2 (mmol/L)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
Medium	0	6	7.49(0.01)	6	39.67(0.56)	6	112.33(7.31)	6	30.00(0.37)	6	31.17(0.48)
	1	6	7.49(0.01)	6	36.02(2.16)	6	80.67(7.39)	6	27.67(1.63)	6	28.67(1.63)
	4	6	7.47(0.01)	6	39.67(2.59)	6	84.83(8.03)	6	28.67(1.45)	6	29.83(1.54)
	8	6	7.43(0.04)	6	43.26(4.04)	6	72.75(9.20)	6	28.33(0.63)	6	29.33(0.76)
	12	4	7.45(0.04)	4	42.41(4.59)	4	67.63(7.93)	4	28.63(1.07)	4	30.13(0.97)
	16	4	7.47(0.02)	4	43.20(7.12)	3	72.00(2.31)	4	26.50(1.50)	4	27.25(1.75)
	20	4	7.49(0.01)	4	37.03(1.82)	4	70.50(2.60)	4	28.00(1.29)	4	29.50(1.55)
	24	3	7.50(0.01)	3	35.77(1.04)	3	75.00(1.53)	3	28.00(1.00)	3	29.33(0.67)
	28	3	7.50(0.02)	3	35.90(2.83)	3	73.33(2.03)	3	28.33(1.20)	3	29.00(1.53)
	32	3	7.51(0.03)	3	34.80(2.33)	3	80.00(6.00)	3	28.00(0.58)	3	29.00(0.58)
	36	3	7.52(0.02)	3	34.57(2.60)	3	88.00(7.94)	3	27.67(0.88)	3	28.67(0.88)
	40	2	7.47(0.00)	2	40.45(2.55)	2	79.00(8.00)	2	29.50(1.50)	2	30.50(1.50)
	44	2	7.48(0.01)	2	32.95(4.55)	2	77.00(2.00)	2	24.50(2.50)	2	26.00(3.00)
	48	2	7.49(0.04)	2	28.35(0.55)	2	86.50(8.50)	2	21.50(2.50)	2	22.50(2.50)
	52	1	7.51(NA)	1	24.70(NA)	1	96.00(NA)	1	20.00(NA)	1	20.00(NA)
	56	2	7.50(0.02)	2	29.15(1.35)	2	97.00(3.00)	2	23.00(0.00)	2	24.00(0.00)
	60	1	7.53(NA)	1	27.40(NA)	1	111.00(NA)	1	23.00(NA)	1	24.00(NA)
	64	2	7.50(0.02)	2	28.40(2.80)	2	99.00(11.00)	2	22.00(1.00)	2	23.00(1.00)
	68	1	7.46(NA)	1	23.05(NA)	1	115.00(NA)	1	16.50(NA)	1	17.50(NA)
High	72	3	7.49(0.01)	3	24.63(3.26)	3	111.33(9.70)	3	18.67(2.19)	3	19.67(2.19)
	0	3	7.56(0.03)	3	33.87(4.53)	3	104.33(9.77)	3	30.00(2.08)	3	31.00(2.65)
	1	3	7.49(0.03)	3	38.27(1.62)	3	93.33(13.92)	3	29.33(1.76)	3	30.33(1.76)
	4	3	7.48(0.05)	3	43.33(5.08)	3	92.00(8.50)	3	31.67(0.33)	3	33.00(0.58)
	8	3	7.33(0.08)	3	61.67(10.68)	3	57.67(20.20)	3	31.33(1.76)	3	33.83(1.88)
Death		6	7.33(0.06)	6	56.10(7.71)	6	47.67(11.91)	6	28.00(1.65)	6	30.00(1.81)

[1] SE=Standard Error

Table 3c. Descriptive Statistics for Oxygen Saturation, Base Excess, Anion Gap, Hemoglobin, and Hematocrit by Study Time Course in Air Control and CG-Exposed Groups.

Group	Study Time Course	Oxygen Saturation (%)		Base Excess (mmol/L)		Anion Gap (mmol/L)		Hemoglobin (g/dL)		Hematocrit (%)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
Control	0	3	96.67(1.20)	3	6.00(2.52)	3	8.00(1.15)	3	9.00(1.00)	3	25.67(2.33)
	1	1	100.00(NA)	1	4.00(NA)	1	7.00(NA)	1	7.00(NA)	1	20.00(NA)
	4	2	98.75(0.25)	3	4.00(0.58)	3	8.67(0.33)	3	8.17(1.17)	3	24.33(2.91)
	8	3	98.00(0.00)	3	5.00(3.00)	3	10.33(1.45)	3	8.67(0.88)	3	25.67(2.33)
	12	3	98.17(0.44)	3	3.83(1.09)	3	10.33(0.88)	3	8.83(0.93)	3	25.67(2.40)
	16	2	98.50(0.50)	2	5.00(0.00)	2	8.50(2.50)	2	9.00(0.00)	2	26.00(1.00)
	20	3	98.33(0.67)	3	2.33(1.45)	3	7.33(1.67)	3	8.00(1.15)	3	23.67(3.18)
	24	3	98.33(0.33)	3	2.00(1.00)	3	8.33(1.76)	3	8.33(1.20)	3	24.00(3.06)
	28	3	97.67(0.33)	3	0.67(1.76)	3	9.00(2.00)	3	8.33(1.86)	3	24.33(4.84)
	32	3	97.33(0.33)	3	2.67(0.88)	3	11.00(0.58)	3	9.33(1.20)	3	27.33(3.84)
	36	2	97.00(0.00)	2	4.50(0.50)	2	11.50(1.50)	2	14.50(1.50)	2	41.50(4.50)
	40	3	97.67(0.67)	3	2.33(2.19)	3	11.00(2.31)	3	8.67(1.33)	3	25.33(3.71)
	44	3	97.67(1.33)	3	0.67(0.88)	3	9.67(1.86)	3	8.00(1.00)	3	23.67(3.33)
	48	3	98.00(1.00)	3	-2.00(3.06)	3	8.33(2.85)	3	9.33(3.84)	3	26.67(11.20)
	52	3	97.00(0.58)	3	1.00(1.15)	3	10.33(1.76)	3	8.33(1.76)	3	24.67(5.24)
	56	3	98.17(0.44)	3	1.83(1.59)	3	10.83(1.17)	3	8.83(1.01)	3	25.33(3.18)
	60	3	98.00(0.58)	3	1.00(1.53)	3	11.00(0.58)	3	8.33(1.20)	3	24.00(3.79)
	64	3	97.67(0.33)	3	0.33(1.45)	3	11.67(0.88)	3	10.33(1.33)	3	30.67(3.67)
	68	3	98.33(0.33)	3	-1.33(2.67)	3	9.67(0.88)	3	7.33(1.45)	3	21.67(4.41)
	72	2	99.00(0.00)	2	-4.00(1.00)	2	9.50(0.50)	2	6.00(1.00)	2	19.00(3.00)
Low	0	2	98.50(0.50)	2	8.00(0.00)	2	6.50(1.50)	2	8.00(1.00)	2	24.00(2.00)
	1	2	95.50(0.50)	2	5.50(0.50)	2	5.50(0.50)	2	7.50(0.50)	2	22.00(1.00)
	4	2	98.50(0.50)	2	10.50(2.50)	2	7.00(1.00)	2	7.50(0.50)	2	23.00(1.00)
	8	2	98.50(0.50)	2	7.00(2.00)	2	9.00(0.00)	2	10.00(0.00)	2	29.00(0.00)
	12	2	96.00(0.00)	2	6.00(0.00)	2	9.50(1.50)	2	8.50(0.50)	2	25.50(1.50)
	16	2	97.00(0.00)	2	4.00(2.00)	2	9.50(2.50)	2	8.00(1.00)	2	23.00(2.00)
	20	2	96.50(0.50)	2	4.50(0.50)	2	11.50(1.50)	2	8.50(0.50)	2	24.50(0.50)
	24	2	93.00(4.00)	2	5.00(1.00)	2	7.50(0.50)	2	8.50(2.50)	2	25.00(6.00)
	28	2	97.50(0.50)	2	5.50(1.50)	2	8.50(0.50)	2	8.00(2.00)	2	24.00(5.00)
	32	2	97.00(2.00)	2	2.50(1.50)	2	8.50(2.50)	2	9.00(3.00)	2	26.50(7.50)
	36	2	96.50(0.50)	2	2.75(0.75)	2	9.75(0.75)	2	9.50(1.00)	2	27.75(3.25)
	40	2	96.50(1.50)	2	3.00(1.00)	2	10.50(2.50)	2	11.00(1.00)	2	32.50(2.50)
	44	2	96.00(0.00)	2	2.50(1.50)	2	11.50(0.50)	2	11.00(1.00)	2	32.50(3.50)
	48	2	92.50(4.50)	2	0.00(2.00)	2	7.00(1.00)	2	8.50(1.50)	2	25.00(4.00)
	52	2	97.50(0.50)	2	-4.00(2.00)	2	9.00(2.00)	2	10.00(3.00)	2	29.50(7.50)
	56	2	98.00(0.00)	2	0.00(0.00)	2	10.50(1.50)	2	11.00(4.00)	2	32.00(11.00)
	60	2	97.50(0.50)	2	2.00(0.00)	2	11.50(1.50)	2	9.00(3.00)	2	26.50(7.50)
	64	2	96.50(1.50)	2	2.00(2.00)	2	8.50(0.50)	2	10.00(1.00)	2	28.50(2.50)
	68	2	95.00(1.00)	2	-5.50(7.50)	2	16.00(4.00)	2	6.00(0.00)	2	18.50(0.50)
	72	2	97.50(1.50)	2	-4.00(2.00)	2	9.00(3.00)	2	10.00(4.00)	2	29.00(11.00)

Table 3c. Descriptive Statistics for Oxygen Saturation, Base Excess, Anion Gap, Hemoglobin, and Hematocrit by Study Time Course in Air Control and CG-Exposed Groups (Continued)

Group	Study Time Course	Oxygen Saturation (%)		Base Excess (mmol/L)		Anion Gap (mmol/L)		Hemoglobin (g/dL)		Hematocrit (%)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
Medium	0	6	98.50(0.34)	6	6.83(0.60)	6	8.83(1.11)	6	8.67(0.42)	6	25.83(1.17)
	1	6	96.00(1.21)	6	4.17(1.68)	6	7.50(1.28)	6	7.00(0.58)	6	20.83(1.54)
	4	6	96.00(1.32)	6	4.83(1.45)	6	5.33(1.84)	6	7.67(0.80)	6	22.83(2.18)
	8	6	88.25(6.00)	6	4.00(0.77)	6	10.42(1.49)	6	8.58(0.71)	6	24.58(1.77)
	12	4	89.13(6.27)	4	4.75(1.11)	4	7.75(1.60)	4	8.25(1.11)	4	24.63(3.09)
	16	3	94.67(0.88)	4	2.50(1.55)	4	5.25(3.33)	4	7.75(0.75)	4	22.00(1.91)
	20	4	95.25(0.25)	4	4.75(1.38)	4	9.50(0.96)	4	7.75(1.11)	4	23.00(3.24)
	24	3	96.00(0.00)	3	4.67(0.88)	2	9.50(0.50)	3	7.67(1.33)	3	22.33(3.71)
	28	3	95.67(0.33)	3	5.00(1.15)	3	8.33(1.20)	3	8.00(1.53)	3	23.67(4.91)
	32	3	96.67(0.67)	3	4.67(0.33)	3	8.67(0.67)	3	8.67(1.86)	3	25.33(4.70)
	36	3	97.67(0.88)	3	5.00(0.58)	3	4.33(4.81)	3	8.67(1.45)	3	25.67(4.67)
	40	2	96.00(1.00)	2	5.50(1.50)	2	7.50(0.50)	2	8.00(2.00)	2	23.00(5.00)
	44	2	96.50(0.50)	2	1.00(3.00)	2	5.00(4.00)	2	6.50(0.50)	2	20.50(1.50)
	48	1	96.00(NA)	2	-2.00(3.00)	2	11.00(4.00)	2	6.00(1.00)	2	17.50(3.50)
	52	1	98.00(NA)	1	-4.00(NA)	1	-5.00(NA)	1	7.00(NA)	1	21.00(NA)
	56	2	98.50(0.50)	2	-0.50(0.50)	2	19.00(8.00)	2	8.00(2.00)	2	23.50(5.50)
	60	1	99.00(NA)	1	0.00(NA)	1	19.00(NA)	1	9.00(NA)	1	25.00(NA)
	64	2	98.00(1.00)	2	-1.00(1.00)	2	17.50(7.50)	2	8.50(0.50)	2	25.50(1.50)
	68	1	99.00(NA)	1	-7.50(NA)	0	NA (NA)	0	NA (NA)	0	NA (NA)
	72	3	98.67(0.33)	3	-4.67(1.86)	2	12.00(2.00)	3	7.33(0.33)	3	21.67(0.67)
High	0	3	98.67(0.33)	3	7.67(1.86)	3	8.67(1.76)	3	8.00(0.58)	3	23.67(2.03)
	1	3	97.33(1.20)	3	5.33(2.19)	3	4.67(0.33)	3	6.33(0.67)	3	19.00(2.08)
	4	3	96.67(1.33)	3	8.33(0.88)	3	8.33(1.45)	3	8.33(1.45)	3	24.33(3.76)
	8	3	67.00(16.09)	3	5.83(2.24)	2	8.50(1.50)	2	8.25(1.25)	2	24.75(2.75)
Death		6	62.67(13.06)	6	2.33(2.09)	5	10.80(1.28)	5	8.20(0.49)	5	24.20(1.16)

[1] SE=Standard Error

Table 4a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Respiratory Rate by Study Time Course in Air Control and CG-Exposed Groups.

Group	Study Time Course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
Control	0	3	34.00(2.52)	3	28.00(3.21)	3	99.33(0.33)	2	158.50(27.50)	3	101.33(6.39)
	1	3	36.00(2.65)	3	29.33(3.71)	3	99.00(1.00)	2	124.00(38.00)	3	100.00(3.21)
	2	3	37.67(3.84)	3	28.67(3.53)	3	99.00(0.58)	2	97.00(3.00)	3	100.67(2.19)
	3	3	43.00(2.00)	3	29.00(3.79)	3	97.33(0.33)	2	103.00(7.00)	3	102.33(3.76)
	4	3	44.00(1.53)	3	28.33(4.10)	3	94.33(1.76)	2	102.00(8.00)	3	102.33(4.33)
	5	3	42.33(0.88)	3	29.00(3.79)	3	96.00(1.53)	1	106.00(NA)	3	101.00(3.79)
	6	3	42.67(0.88)	3	31.67(1.76)	3	98.00(0.58)	2	101.00(0.00)	3	102.00(0.58)
	7	3	44.00(2.08)	3	32.00(1.53)	3	99.33(0.33)	2	114.50(11.50)	3	110.67(8.21)
	8	3	41.33(1.45)	3	30.33(0.33)	3	98.00(0.58)	1	104.00(NA)	3	103.33(5.55)
	9	3	41.00(1.15)	3	30.00(0.00)	3	96.33(2.73)	2	97.50(6.50)	3	105.67(8.41)
	10	3	40.33(1.45)	3	30.33(0.33)	3	98.33(0.88)	2	102.00(6.00)	3	98.67(5.93)
	11	2	41.50(3.50)	2	30.00(0.00)	2	98.00(1.00)	2	104.00(9.00)	2	104.00(9.00)
	12	3	40.33(1.86)	3	30.33(0.33)	3	99.00(0.58)	2	112.00(14.00)	3	105.33(11.14)
	13	3	40.00(1.00)	3	30.00(0.00)	3	95.33(2.19)	2	107.50(4.50)	3	103.00(3.00)
	14	3	39.00(1.00)	3	30.33(0.33)	3	98.67(0.33)	2	103.50(2.50)	3	104.00(3.00)
	15	3	40.00(1.73)	3	30.33(0.33)	3	96.67(1.20)	2	106.00(4.00)	3	107.67(5.67)
	16	3	38.33(0.88)	3	30.33(0.33)	3	98.67(0.88)	2	106.00(12.00)	3	99.00(11.02)
	17	3	38.00(0.58)	3	30.33(0.33)	3	98.00(0.58)	2	99.50(6.50)	3	94.00(6.66)
	18	3	36.67(1.20)	3	30.33(0.33)	3	97.67(0.67)	2	105.00(8.00)	3	99.00(7.57)
	19	3	35.67(0.88)	3	30.33(0.33)	3	97.67(1.20)	2	88.00(3.00)	3	92.67(4.41)
	20	3	36.33(1.45)	3	30.33(0.33)	3	99.00(0.58)	2	89.00(11.00)	3	87.67(9.82)
	21	3	37.33(0.33)	3	30.00(0.00)	3	95.67(3.84)	2	102.00(2.00)	3	99.00(2.08)
	22	3	37.67(0.33)	3	30.33(0.33)	3	98.00(1.15)	2	95.50(3.50)	3	101.67(5.36)
	23	3	37.33(0.33)	3	30.00(0.58)	3	96.33(2.03)	1	110.00(NA)	3	109.33(0.67)
	24	3	35.67(0.33)	3	30.00(0.58)	3	99.00(0.58)	2	97.00(6.00)	3	98.00(3.00)
	25	3	35.33(0.33)	3	30.33(0.33)	3	99.00(0.58)	2	86.50(6.50)	3	96.00(3.46)
	26	3	35.67(0.88)	3	30.00(0.58)	3	96.33(3.18)	2	94.00(16.00)	3	102.00(6.11)
	27	3	35.67(1.20)	3	30.00(0.58)	3	97.33(1.45)	2	99.00(16.00)	3	99.33(9.24)
	28	3	35.00(0.58)	3	30.33(0.33)	3	94.00(3.21)	2	90.50(7.50)	3	91.33(5.24)
	29	3	35.67(0.67)	3	30.33(0.33)	3	98.67(0.88)	2	96.00(6.00)	3	100.33(6.12)
	30	3	36.33(1.33)	3	30.00(0.00)	3	98.00(1.00)	2	95.50(0.50)	3	96.33(1.45)
	31	2	37.50(0.50)	2	30.50(0.50)	2	97.00(2.00)	1	115.00(NA)	2	99.00(14.00)
	32	3	37.00(1.53)	3	29.67(0.33)	3	92.00(3.21)	2	94.75(12.25)	3	97.67(6.01)
	33	3	36.67(0.33)	3	30.00(0.58)	3	97.00(1.53)	2	100.50(3.50)	3	101.33(1.45)
	34	3	36.33(0.33)	3	30.00(0.58)	3	96.67(1.86)	2	103.50(0.50)	3	100.00(5.00)
	35	3	35.00(1.15)	3	30.33(0.33)	3	98.00(1.00)	2	89.00(4.00)	3	89.33(2.19)
	36	3	35.00(1.00)	3	30.00(0.00)	3	96.67(1.33)	2	86.50(1.50)	3	87.33(1.86)
	37	3	33.00(1.15)	3	30.00(0.00)	3	99.00(0.58)	2	79.00(5.00)	3	80.67(2.85)
	38	3	33.00(0.58)	3	30.00(0.00)	3	95.67(1.86)	2	78.50(3.50)	3	81.67(3.76)
	39	3	34.33(1.45)	3	30.33(0.33)	3	94.67(1.76)	2	88.00(0.00)	3	92.00(4.04)
	40	3	34.33(0.88)	3	30.33(0.33)	3	94.33(2.03)	2	90.00(2.00)	3	92.67(2.96)
	41	3	34.67(1.20)	3	30.67(0.33)	3	97.33(0.33)	2	80.50(5.50)	3	85.33(5.78)
	42	3	35.00(2.08)	3	30.00(0.00)	3	94.33(2.67)	1	78.00(NA)	3	86.67(5.24)
	43	3	34.00(1.73)	3	30.00(0.00)	3	97.33(0.67)	1	78.00(NA)	3	85.67(5.36)
	44	3	33.33(1.45)	3	30.00(0.00)	3	95.67(0.33)	2	79.00(1.00)	3	82.67(4.18)

Table 4a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Respiratory Rate by Study Time Course in Air Control and CG-Exposed Groups (Continued)

Group	Study Time Course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
Control	45	3	32.67(1.33)	3	30.00(0.00)	3	96.67(1.86)	2	76.50(1.50)	3	75.00(1.73)
	46	3	33.00(1.73)	3	30.67(0.33)	3	99.00(0.00)	2	76.00(1.00)	3	78.00(2.08)
	47	3	33.33(1.76)	3	30.33(0.33)	3	98.00(0.58)	2	77.00(2.00)	3	81.00(4.16)
	48	3	33.00(1.15)	3	30.33(0.33)	3	96.67(1.20)	2	75.50(0.50)	3	81.33(5.84)
	49	3	32.33(0.88)	3	30.33(0.33)	3	96.33(2.73)	2	75.00(3.00)	3	77.33(3.48)
	50	2	33.00(2.00)	2	30.50(0.50)	2	94.00(4.00)	1	78.00(NA)	2	84.50(5.50)
	51	3	33.67(0.88)	3	30.67(0.33)	3	97.00(0.58)	2	80.50(2.50)	3	81.67(1.33)
	52	3	34.00(1.15)	3	32.00(1.53)	3	97.00(1.53)	2	79.50(0.50)	3	83.00(3.51)
	53	3	33.67(2.19)	3	31.67(1.20)	3	96.67(1.86)	2	74.50(3.50)	3	85.00(10.69)
	54	3	34.00(2.00)	3	32.33(1.86)	3	97.33(0.33)	2	76.00(0.00)	3	84.00(8.00)
	55	3	34.00(2.89)	3	31.67(1.20)	3	96.33(2.73)	2	75.00(1.00)	3	85.67(10.17)
	56	3	32.50(2.18)	3	32.17(1.69)	3	98.00(1.53)	2	72.50(1.50)	3	80.33(7.88)
	57	3	32.67(2.19)	3	32.33(1.86)	3	97.67(1.86)	2	70.50(2.50)	3	76.67(5.78)
	58	2	32.50(2.50)	2	33.00(3.00)	2	98.50(1.50)	1	78.00(NA)	2	77.00(1.00)
	59	1	33.50(NA)	1	32.50(NA)	1	98.50(NA)	0	NA (NA)	1	88.00(NA)
	60	3	32.00(2.00)	3	32.00(1.53)	3	95.00(2.65)	2	74.50(3.50)	3	79.00(3.51)
	61	3	32.00(2.00)	3	32.00(2.00)	3	97.67(1.45)	2	71.00(1.00)	3	72.00(1.15)
	62	3	31.33(1.20)	3	31.67(1.67)	3	98.33(0.88)	2	70.00(0.00)	3	74.00(4.00)
	63	3	31.33(1.76)	3	31.67(2.19)	3	95.67(1.76)	2	75.00(2.00)	3	74.67(1.20)
	64	3	31.33(1.45)	3	31.67(2.19)	3	98.33(0.88)	2	73.00(1.00)	3	75.33(2.03)
	65	3	30.67(1.76)	3	31.67(2.19)	3	98.00(1.53)	2	67.00(4.00)	3	72.33(2.40)
	66	3	30.67(1.76)	3	31.67(2.19)	3	98.00(1.00)	2	68.00(4.00)	3	73.33(2.03)
	67	3	30.67(1.76)	3	31.67(2.19)	3	396.33(299.8)	2	69.50(1.50)	3	70.00(0.58)
	68	3	30.67(2.33)	3	31.67(2.19)	3	96.00(2.00)	2	70.50(1.50)	3	72.67(2.73)
	69	3	30.33(2.40)	3	31.67(2.19)	3	95.33(1.86)	2	68.00(1.00)	3	71.33(3.38)
	70	2	178.50(151.5)	2	29.50(0.50)	2	95.50(2.50)	2	69.00(1.00)	2	70.00(2.00)
	71	1	31.00(NA)	1	30.00(NA)	1	99.00(NA)	1	70.00(NA)	1	70.00(NA)
	72	1	31.00(NA)	1	31.00(NA)	1	95.00(NA)	1	74.00(NA)	1	73.00(NA)
Low	0	2	36.00(5.00)	2	25.00(3.00)	1	97.00(NA)	0	NA (NA)	2	115.00(9.00)
	1	2	40.00(3.00)	2	29.50(1.50)	2	97.00(3.00)	0	NA (NA)	2	109.50(9.50)
	2	2	45.00(1.00)	2	32.00(1.00)	2	97.00(2.00)	0	NA (NA)	2	102.50(9.50)
	3	2	45.00(2.00)	2	31.00(0.00)	2	99.00(1.00)	0	NA (NA)	2	103.50(1.50)
	4	2	43.50(1.50)	2	31.50(0.50)	2	99.50(0.50)	0	NA (NA)	2	103.00(3.00)
	5	2	44.00(3.00)	2	33.50(3.50)	2	99.00(1.00)	0	NA (NA)	2	106.00(11.00)
	6	2	54.50(5.50)	2	33.00(4.00)	2	89.50(8.50)	0	NA (NA)	2	186.50(53.50)
	7	2	53.50(0.50)	2	32.50(4.50)	2	92.50(7.50)	0	NA (NA)	2	209.00(46.00)
	8	2	40.50(0.50)	2	39.50(5.50)	2	98.00(1.00)	0	NA (NA)	2	155.00(7.00)
	9	2	38.50(0.50)	2	31.00(1.00)	2	96.00(4.00)	0	NA (NA)	2	190.00(19.00)
	10	2	36.50(3.50)	2	32.00(0.00)	2	96.50(3.50)	0	NA (NA)	2	114.50(2.50)
	11	2	38.00(2.00)	2	32.00(1.00)	2	96.00(0.00)	0	NA (NA)	2	123.00(16.00)
	12	2	38.00(1.00)	2	32.50(0.50)	2	97.00(0.00)	0	NA (NA)	2	125.00(26.00)
	13	2	39.00(3.00)	2	32.00(1.00)	2	95.50(1.50)	0	NA (NA)	2	120.00(29.00)
	14	2	38.00(3.00)	2	31.50(0.50)	2	97.00(1.00)	0	NA (NA)	2	114.50(24.50)
	15	2	37.00(2.00)	2	31.50(1.50)	2	96.00(0.00)	0	NA (NA)	2	137.00(1.00)

Table 4a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Respiratory Rate by Study Time Course in Air Control and CG-Exposed Groups (Continued)

Group	Study Time Course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
Low	16	2	36.00(0.00)	2	31.50(1.50)	2	97.50(0.50)	0	NA (NA)	2	129.00(8.00)
	17	2	38.00(0.00)	2	32.00(2.00)	2	96.50(0.50)	0	NA (NA)	2	110.50(25.50)
	18	2	38.00(0.00)	2	32.50(1.50)	2	96.50(0.50)	0	NA (NA)	2	116.50(8.50)
	19	2	36.50(1.50)	2	32.00(1.00)	2	94.50(1.50)	0	NA (NA)	2	133.00(17.00)
	20	2	35.00(0.00)	2	32.00(1.00)	2	98.00(2.00)	0	NA (NA)	2	110.50(0.50)
	21	2	35.50(0.50)	2	32.00(1.00)	2	98.50(0.50)	0	NA (NA)	2	121.00(7.00)
	22	2	36.00(0.00)	2	32.00(1.00)	2	92.50(5.50)	0	NA (NA)	2	107.50(4.50)
	23	2	37.00(1.00)	2	32.50(1.50)	2	96.50(0.50)	0	NA (NA)	2	114.50(8.50)
	24	2	35.50(0.50)	2	32.00(1.00)	2	94.00(3.00)	0	NA (NA)	2	113.50(6.50)
	25	2	34.00(1.00)	2	32.00(1.00)	2	94.00(4.00)	0	NA (NA)	2	95.50(6.50)
	26	2	35.50(0.50)	2	32.00(0.00)	2	90.50(6.50)	0	NA (NA)	2	117.50(6.50)
	27	2	36.50(1.50)	2	31.50(0.50)	2	96.00(1.00)	0	NA (NA)	2	119.00(0.00)
	28	2	37.50(0.50)	2	32.50(1.50)	2	91.00(2.00)	0	NA (NA)	2	123.00(0.00)
	29	2	36.50(1.50)	2	32.50(1.50)	2	90.50(0.50)	0	NA (NA)	2	119.00(1.00)
	30	2	35.50(2.50)	2	32.50(1.50)	2	92.00(2.00)	0	NA (NA)	2	131.50(2.50)
	31	2	37.00(2.00)	2	31.00(0.00)	2	95.00(2.00)	0	NA (NA)	2	127.50(6.50)
	32	2	38.50(1.50)	2	32.50(1.50)	2	96.00(2.00)	0	NA (NA)	2	124.00(2.00)
	33	2	37.00(1.00)	2	31.00(0.00)	2	90.50(0.50)	0	NA (NA)	2	127.00(1.00)
	34	2	37.00(2.00)	2	34.50(0.50)	2	98.00(1.00)	0	NA (NA)	2	149.50(32.50)
	35	2	35.50(0.50)	2	32.00(0.00)	2	95.00(3.00)	0	NA (NA)	2	121.00(6.00)
	36	2	35.00(0.00)	2	32.50(0.50)	2	95.00(1.00)	0	NA (NA)	2	115.00(1.00)
	37	2	37.50(1.50)	2	32.00(0.00)	2	93.50(1.50)	0	NA (NA)	2	96.00(21.00)
	38	2	39.50(3.50)	2	30.50(1.50)	2	94.00(4.00)	0	NA (NA)	2	101.50(26.50)
	39	2	35.50(0.50)	2	31.50(0.50)	2	93.00(1.00)	0	NA (NA)	2	107.50(7.50)
	40	2	35.50(0.50)	2	31.50(0.50)	2	95.00(3.00)	0	NA (NA)	2	114.50(7.50)
	41	2	35.50(0.50)	2	31.50(0.50)	2	90.50(3.50)	0	NA (NA)	2	127.00(16.00)
	42	2	34.50(0.50)	2	31.00(1.00)	2	97.50(0.50)	0	NA (NA)	2	122.00(15.00)
	43	2	39.50(0.50)	2	32.00(1.00)	2	96.50(0.50)	0	NA (NA)	2	112.00(8.00)
	44	2	41.00(0.00)	2	32.00(1.00)	1	96.00(NA)	0	NA (NA)	2	106.50(1.50)
	45	2	37.50(0.50)	2	31.50(1.50)	2	91.00(0.00)	0	NA (NA)	2	105.50(4.50)
	46	2	38.50(0.50)	2	31.50(1.50)	2	95.00(0.00)	0	NA (NA)	2	104.00(7.00)
	47	2	37.50(3.50)	2	31.00(2.00)	2	91.00(0.00)	0	NA (NA)	2	104.50(10.50)
	48	2	38.00(3.00)	2	31.00(2.00)	2	93.00(0.00)	0	NA (NA)	2	106.50(10.50)
	49	2	38.00(2.00)	2	32.00(3.00)	1	90.00(NA)	0	NA (NA)	2	125.00(13.00)
	50	2	28.00(8.00)	2	31.50(3.50)	2	88.00(4.00)	0	NA (NA)	2	137.00(26.00)
	51	2	22.50(22.50)	2	64.00(28.00)	2	89.00(6.00)	0	NA (NA)	2	157.50(51.50)
	52	2	43.50(3.50)	2	33.00(2.00)	2	88.50(1.50)	0	NA (NA)	2	133.50(34.50)
	53	2	41.50(0.50)	2	33.50(0.50)	2	89.50(1.50)	0	NA (NA)	2	122.50(20.50)
	54	2	40.50(2.50)	2	34.50(0.50)	2	89.50(7.50)	0	NA (NA)	2	137.00(1.00)
	55	2	38.50(1.50)	2	34.50(0.50)	2	87.50(3.50)	0	NA (NA)	2	117.50(2.50)
	56	2	36.00(1.00)	2	35.00(1.00)	2	92.50(2.50)	0	NA (NA)	2	103.00(5.00)
	57	2	37.50(0.50)	2	33.50(0.50)	2	95.50(3.50)	0	NA (NA)	2	75.00(21.00)
	58	2	38.50(1.50)	2	33.50(0.50)	2	95.50(1.50)	0	NA (NA)	2	119.50(2.50)
	59	2	38.50(2.50)	2	32.50(1.50)	2	95.00(4.00)	0	NA (NA)	2	114.00(8.00)

Table 4a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Respiratory Rate by Study Time Course in Air Control and CG-Exposed Groups (Continued)

Group	Study Time Course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
Low	60	2	38.50(1.50)	2	33.00(1.00)	2	96.00(4.00)	0	NA (NA)	2	108.50(3.50)
	61	2	38.00(2.00)	2	32.00(2.00)	2	99.00(1.00)	0	NA (NA)	2	97.00(6.00)
	62	2	37.00(4.00)	2	32.00(2.00)	2	99.50(0.50)	0	NA (NA)	2	112.50(6.50)
	63	2	38.00(4.00)	2	32.00(2.00)	2	99.50(0.50)	0	NA (NA)	2	106.00(1.00)
	64	2	37.50(2.50)	2	30.50(1.50)	2	97.50(0.50)	0	NA (NA)	2	107.00(9.00)
	65	2	37.00(2.00)	2	30.00(1.00)	2	98.00(0.00)	0	NA (NA)	2	104.50(5.50)
	66	2	37.00(1.00)	2	31.00(2.00)	2	98.00(0.00)	0	NA (NA)	2	107.00(10.00)
	67	2	38.00(0.00)	2	31.50(1.50)	2	98.00(2.00)	0	NA (NA)	2	106.00(4.00)
	68	2	37.00(0.00)	2	31.00(1.00)	2	97.50(2.50)	0	NA (NA)	2	102.00(9.00)
	69	2	36.50(1.50)	2	31.00(1.00)	2	98.50(0.50)	0	NA (NA)	2	100.00(10.00)
	70	2	35.50(1.50)	2	31.50(1.50)	2	98.50(1.50)	0	NA (NA)	2	84.50(3.50)
	71	2	35.00(2.00)	2	31.50(1.50)	2	98.00(2.00)	0	NA (NA)	2	84.50(0.50)
	72	1	33.00(NA)	1	29.00(NA)	1	100.00(NA)	0	NA (NA)	1	55.00(NA)
Medium	0	6	39.33(2.60)	6	26.17(1.68)	5	95.80(1.80)	3	123.33(8.51)	5	117.80(6.97)
	1	6	38.67(2.34)	6	29.67(0.87)	6	96.08(0.99)	3	102.00(4.16)	6	101.83(5.29)
	2	6	41.17(2.24)	6	30.33(0.71)	6	96.83(1.22)	4	104.00(6.89)	6	104.33(5.14)
	3	6	42.75(1.92)	6	30.33(0.71)	6	95.33(1.94)	4	108.25(5.39)	6	111.50(3.17)
	4	6	44.25(1.58)	6	30.33(0.84)	6	96.83(0.98)	4	134.00(21.75)	6	111.33(3.64)
	5	6	42.00(1.75)	6	30.33(0.71)	6	97.17(0.83)	4	130.00(17.44)	6	115.50(5.54)
	6	6	44.83(2.23)	6	30.17(0.79)	6	94.67(2.80)	4	131.75(13.99)	6	142.67(11.75)
	7	6	48.83(5.42)	6	29.00(0.63)	6	89.67(5.17)	4	153.00(34.21)	6	154.50(21.85)
	8	5	41.80(1.07)	5	29.60(0.51)	5	93.20(2.13)	3	150.00(20.98)	5	141.60(12.10)
	9	5	31.80(7.02)	5	30.00(0.32)	4	97.75(0.85)	3	110.33(45.94)	4	122.25(5.79)
	10	4	42.00(3.32)	4	29.25(0.85)	4	93.25(2.78)	2	150.50(35.50)	4	141.75(15.51)
	11	4	43.50(3.38)	4	31.00(1.08)	4	96.25(0.75)	2	145.00(30.00)	4	143.00(13.70)
	12	4	43.00(3.49)	4	30.50(0.65)	4	95.25(1.18)	2	166.50(53.50)	4	154.75(23.86)
	13	4	39.25(1.89)	4	30.50(0.29)	4	92.75(1.65)	1	169.00(NA)	4	133.50(10.94)
	14	4	37.75(2.29)	4	30.25(0.48)	4	90.50(1.89)	2	139.50(8.50)	4	135.50(7.60)
	15	4	39.75(3.07)	4	30.25(0.48)	4	91.25(3.84)	1	137.00(NA)	4	142.50(5.85)
	16	4	40.25(3.40)	4	30.00(0.71)	4	92.00(1.58)	1	144.00(NA)	4	139.25(7.55)
	17	4	38.75(2.02)	4	30.50(0.65)	4	93.00(1.15)	1	134.00(NA)	4	130.50(7.41)
	18	4	41.00(2.35)	4	29.75(0.95)	4	88.75(1.93)	2	138.50(1.50)	4	135.75(4.87)
	19	4	41.00(1.73)	4	30.25(0.25)	4	92.75(1.03)	2	136.00(6.00)	4	138.25(2.32)
	20	3	41.67(1.67)	3	30.67(0.33)	3	96.33(0.33)	2	125.50(3.50)	3	134.33(5.33)
	21	3	40.33(1.45)	3	30.33(0.33)	3	95.67(1.33)	2	113.50(11.50)	3	123.67(7.75)
	22	3	40.67(1.76)	3	30.00(0.58)	3	92.33(1.67)	2	124.50(12.50)	3	127.33(8.76)
	23	3	40.33(2.60)	3	29.67(0.33)	3	93.33(2.73)	2	105.00(14.00)	3	125.33(16.83)
	24	3	41.33(2.85)	3	30.33(0.33)	3	92.67(1.20)	1	99.00(NA)	3	127.00(14.57)
	25	3	38.67(0.33)	3	30.33(0.33)	3	98.33(0.67)	2	96.50(16.50)	3	121.33(6.17)
	26	3	40.67(1.76)	3	30.00(0.58)	3	97.67(0.33)	2	119.50(1.50)	3	131.67(8.67)
	27	3	41.00(1.53)	3	30.00(0.58)	3	94.00(2.65)	2	125.00(3.00)	3	127.33(2.73)
	28	3	38.67(1.76)	3	30.33(0.33)	3	93.67(2.60)	2	131.50(8.50)	3	128.67(5.17)
	29	3	39.00(1.53)	3	30.00(0.58)	3	95.33(2.33)	1	117.00(NA)	3	122.00(3.21)

Table 4a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Respiratory Rate by Study Time Course in Air Control and CG-Exposed Groups (Continued)

Group	Study Time Course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
Medium	30	3	35.33(3.18)	3	30.00(0.58)	3	95.33(1.33)	2	124.00(5.00)	3	121.67(2.67)
	31	3	39.33(2.33)	3	29.33(0.33)	3	95.33(0.88)	1	110.00(NA)	3	118.00(4.62)
	32	3	37.67(1.76)	3	30.33(0.88)	3	94.67(0.67)	1	121.00(NA)	3	122.67(2.19)
	33	3	37.33(1.45)	3	30.00(0.58)	3	95.67(1.20)	1	137.00(NA)	3	125.67(6.64)
	34	3	36.33(3.28)	3	30.33(0.88)	3	92.67(2.73)	2	120.00(3.00)	3	118.67(4.48)
	35	3	35.67(1.76)	3	30.00(1.00)	3	95.33(0.67)	2	115.00(14.00)	3	111.67(8.74)
	36	3	37.00(0.58)	3	30.33(0.88)	3	95.00(0.58)	2	101.50(1.50)	3	109.33(5.49)
	37	3	36.00(2.52)	3	31.00(0.58)	3	96.33(2.73)	2	99.50(0.50)	3	98.33(1.67)
	38	3	37.67(2.40)	3	30.33(0.67)	3	94.00(2.52)	2	103.00(4.00)	3	99.67(3.48)
	39	3	38.33(2.91)	3	30.00(0.58)	3	97.67(0.67)	2	100.00(2.00)	3	98.33(2.40)
	40	2	40.00(2.00)	2	31.00(1.00)	2	95.50(2.50)	1	98.00(NA)	2	95.50(2.50)
	41	3	37.00(2.65)	3	31.00(0.58)	3	96.83(1.01)	2	100.50(1.50)	3	97.00(4.16)
	42	3	36.33(2.96)	3	31.00(0.58)	3	96.67(1.20)	2	97.50(5.50)	3	96.67(3.28)
	43	3	36.00(4.16)	3	30.00(0.58)	3	98.00(0.58)	2	91.50(4.50)	3	94.67(4.10)
	44	3	38.00(6.11)	3	29.33(0.88)	3	98.33(1.20)	2	99.50(3.50)	3	102.67(4.33)
	45	3	32.00(1.53)	3	30.33(0.33)	3	98.33(0.88)	2	93.50(5.50)	3	93.67(6.17)
	46	3	32.33(2.33)	3	30.33(0.33)	3	97.00(2.08)	2	93.00(12.00)	3	93.67(7.22)
	47	3	30.00(1.53)	3	30.67(0.33)	3	98.67(0.88)	2	92.50(12.50)	3	91.67(8.57)
	48	3	31.67(1.45)	3	30.33(0.33)	3	97.67(1.45)	2	91.50(4.50)	3	92.00(2.52)
	49	3	30.33(1.45)	3	30.67(0.33)	3	97.00(1.15)	2	86.00(8.00)	3	86.33(4.48)
	50	3	32.33(2.19)	3	30.00(0.58)	3	97.33(0.88)	2	93.00(2.00)	3	90.67(1.20)
	51	3	32.00(2.65)	3	30.33(0.33)	3	96.33(0.88)	2	86.00(4.00)	3	95.67(9.94)
	52	3	32.00(2.65)	3	29.00(2.00)	3	96.00(2.31)	2	89.00(11.00)	3	98.00(11.27)
	53	3	30.00(1.53)	3	28.67(2.33)	3	95.67(2.60)	2	85.50(10.50)	3	91.00(8.14)
	54	3	32.67(2.33)	3	35.00(4.00)	3	92.67(4.06)	2	94.00(19.00)	3	94.67(15.84)
	55	3	30.67(1.20)	3	31.33(0.33)	3	98.33(1.20)	2	84.50(7.50)	3	85.67(4.33)
	56	3	30.00(1.15)	3	30.67(0.67)	3	95.00(0.00)	2	83.50(6.50)	3	88.00(5.86)
	57	3	29.33(0.88)	3	31.00(0.00)	3	98.33(1.20)	2	83.00(7.00)	3	84.33(4.26)
	58	3	30.67(2.67)	3	31.00(0.00)	3	96.67(2.33)	2	82.50(7.50)	3	85.67(5.33)
	59	3	31.00(3.51)	3	30.67(0.33)	3	95.67(2.85)	2	78.50(5.50)	3	81.67(5.24)
	60	3	31.33(3.84)	3	31.00(0.00)	3	96.00(1.73)	2	77.50(4.50)	3	83.00(6.08)
	61	3	31.33(4.33)	3	31.00(0.00)	3	94.33(3.71)	2	75.00(6.00)	3	78.67(5.46)
	62	3	30.67(3.67)	3	31.00(0.00)	3	98.00(0.58)	2	82.00(12.00)	3	84.00(7.55)
	63	3	31.67(4.18)	3	30.67(0.33)	3	96.67(1.20)	2	87.00(13.00)	3	89.67(8.41)
	64	3	31.00(3.51)	3	31.00(0.00)	3	98.00(1.00)	2	83.00(15.00)	3	86.67(9.40)
	65	3	29.67(2.73)	3	31.00(0.00)	3	97.67(1.45)	2	84.00(17.00)	3	81.33(10.17)
	66	3	30.00(3.06)	3	31.00(0.00)	3	98.67(0.67)	2	81.50(12.50)	3	79.33(6.74)
	67	3	32.33(3.48)	3	31.00(0.00)	3	95.33(1.20)	2	90.00(21.00)	3	91.00(12.42)
	68	3	30.67(3.71)	3	31.00(0.00)	3	96.67(1.45)	2	79.50(10.50)	3	87.67(9.96)
	69	3	29.00(3.00)	3	31.00(0.00)	3	96.00(1.00)	2	75.50(12.50)	3	78.67(7.88)
	70	3	28.67(2.19)	3	31.00(0.00)	3	97.67(1.33)	2	81.00(12.00)	3	79.33(8.41)
	71	3	28.33(2.60)	3	31.00(0.00)	3	94.67(2.96)	2	85.00(10.00)	3	82.67(6.33)
	72	1	34.00(NA)	1	31.00(NA)	1	95.00(NA)	0	NA (NA)	1	85.00(NA)

Table 4a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Respiratory Rate by Study Time Course in Air Control and CG-Exposed Groups (Continued)

Group	Study Time Course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]
High	0	3	38.33(0.88)	3	26.00(2.52)	3	96.00(0.58)	1	98.00(NA)	3	91.33(4.10)
	1	3	40.00(0.58)	3	30.00(0.58)	3	99.00(0.58)	2	85.50(5.50)	3	91.00(5.51)
	2	3	46.33(2.19)	3	28.00(1.00)	3	95.67(1.45)	2	104.50(4.50)	3	106.00(3.46)
	3	3	46.33(2.03)	3	28.33(0.67)	3	96.67(0.88)	2	108.00(4.00)	3	107.67(3.76)
	4	3	51.00(3.06)	3	29.00(0.58)	3	94.67(1.33)	2	151.50(1.50)	3	143.00(16.82)
	5	3	50.67(5.21)	3	28.00(1.00)	3	93.67(3.53)	2	199.50(42.50)	3	168.00(46.31)
	6	2	23.00(17.00)	2	29.50(0.50)	2	100.00(0.00)	1	79.00(NA)	2	63.50(36.50)
	7	1	38.00(NA)	1	29.00(NA)	1	100.00(NA)	0	NA (NA)	1	120.00(NA)
	8	1	39.00(NA)	1	29.00(NA)	1	98.00(NA)	0	NA (NA)	1	108.00(NA)
	9	1	3.00(NA)	1	30.00(NA)	1	84.00(NA)	0	NA (NA)	0	NA (NA)
Death		6	27.00(10.57)	6	29.67(0.42)	5	89.20(4.21)	4	130.00(49.29)	4	141.50(46.72)

[1] SE=Standard Error

Table 4b. Descriptive Statistics for Pulse Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Study Time Course in Air Control and CG-Exposed Groups.

Group	Study Time Course	Respiratory Rate (Breaths/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)1	N	Mean (SE)[1]
Control	2	3	13.33(0.88)	3	20.93(2.23)	3	107.00(6.66)	3	58.33(1.67)	3	75.67(2.96)
	3	3	13.00(1.15)	3	21.60(1.37)	3	106.33(8.21)	3	56.00(0.58)	3	73.33(2.73)
	4	3	13.33(0.88)	3	19.73(1.71)	3	100.67(4.06)	3	39.00(11.53)	3	69.00(2.52)
	5	3	13.33(0.88)	3	19.53(1.60)	3	98.00(6.51)	3	57.00(4.58)	3	64.67(3.76)
	6	3	13.33(0.88)	3	19.67(1.48)	3	108.67(20.67)	3	60.00(15.18)	3	76.33(17.95)
	7	3	13.33(0.88)	3	19.97(1.24)	3	119.00(9.02)	3	66.67(3.84)	3	85.67(6.44)
	8	3	13.33(0.88)	3	19.77(2.06)	3	99.67(7.62)	3	52.33(6.69)	3	67.67(8.09)
	9	3	13.33(0.88)	3	19.33(1.88)	3	112.67(12.41)	3	65.33(12.72)	3	84.67(14.84)
	10	3	13.33(0.88)	3	20.00(1.13)	3	104.33(13.09)	3	58.33(8.35)	3	72.67(12.20)
	11	2	14.00(1.00)	2	20.70(1.90)	2	107.00(18.00)	2	57.50(14.50)	2	74.50(17.50)
	12	3	13.33(0.88)	3	19.53(1.47)	3	92.33(11.32)	3	59.67(5.04)	3	71.67(5.55)
	13	3	13.33(0.88)	3	19.40(2.08)	3	112.33(15.39)	3	66.00(13.65)	3	82.67(14.75)
	14	3	13.33(0.88)	3	20.37(1.27)	3	99.00(8.14)	3	64.33(3.76)	3	75.67(4.81)
	15	3	13.33(0.88)	3	20.53(1.20)	3	107.33(8.88)	3	68.67(15.39)	3	81.33(13.53)
	16	3	13.33(0.88)	3	19.70(1.56)	3	101.33(11.02)	3	55.33(7.33)	3	71.00(9.54)
	17	3	13.33(0.88)	3	19.43(1.88)	3	98.33(15.90)	3	54.33(12.12)	3	70.00(14.19)
	18	3	13.33(0.88)	3	19.40(1.55)	3	100.00(3.61)	3	59.00(9.61)	3	75.00(8.33)
	19	3	13.33(0.88)	3	19.40(1.63)	3	101.00(10.50)	3	59.67(14.85)	3	74.33(14.90)
	20	3	13.33(0.88)	3	19.30(2.16)	3	98.67(8.57)	3	50.33(4.84)	3	67.00(7.09)
	21	3	13.00(1.15)	3	19.13(2.15)	3	115.33(17.07)	3	68.33(15.32)	3	84.33(16.80)
	22	3	13.00(1.15)	3	18.73(2.12)	3	108.67(13.87)	3	61.00(12.50)	3	79.67(14.53)
	23	3	13.33(0.88)	3	19.00(1.88)	3	113.33(15.45)	3	69.00(12.22)	3	85.33(12.84)
	24	3	13.00(1.15)	3	18.87(2.09)	3	108.00(8.08)	3	57.67(6.98)	3	74.67(7.69)
	25	3	13.00(1.15)	3	18.53(1.89)	3	108.67(7.22)	3	59.33(6.77)	3	71.33(8.35)
	26	3	13.00(1.15)	3	18.87(1.91)	3	108.00(6.24)	3	66.67(10.35)	3	82.00(9.07)
	27	3	13.00(1.15)	3	19.47(2.37)	3	112.67(5.24)	3	69.67(13.92)	3	84.67(10.97)
	28	3	12.67(1.45)	3	19.40(2.41)	3	113.67(6.12)	3	73.33(12.98)	3	88.67(10.27)
	29	3	12.67(1.45)	3	18.70(1.91)	3	118.00(7.37)	3	72.00(12.66)	3	90.00(10.02)
	30	3	12.67(1.45)	3	18.53(1.90)	3	111.67(9.74)	3	61.00(9.07)	3	80.00(9.50)
	31	2	12.50(2.50)	2	17.10(2.00)	2	113.50(18.50)	2	72.00(24.00)	2	87.50(22.50)
	32	3	12.67(1.45)	3	18.33(2.30)	3	120.33(10.73)	3	82.00(19.14)	3	95.67(15.56)
	33	3	12.67(1.45)	3	18.07(1.90)	3	124.33(7.88)	3	71.33(7.97)	3	89.67(8.17)
	34	3	12.67(1.45)	3	18.20(1.82)	3	105.33(17.85)	3	60.33(14.44)	3	75.33(14.97)
	35	3	13.33(0.88)	3	18.83(1.73)	3	97.67(13.72)	3	53.00(11.72)	3	67.67(13.69)
	36	3	12.67(1.45)	3	17.97(1.77)	3	106.33(10.40)	3	56.00(10.97)	3	73.67(12.17)
	37	3	12.67(1.45)	3	17.30(1.85)	3	97.33(14.45)	3	51.33(12.24)	3	67.33(14.19)
	38	3	12.67(1.45)	3	17.13(1.87)	3	92.33(9.67)	3	52.33(11.29)	3	67.67(11.70)
	39	3	12.67(1.45)	3	17.70(1.76)	3	113.67(4.41)	3	64.33(6.49)	3	83.00(6.66)
	40	3	12.67(1.45)	3	17.33(1.88)	3	110.67(6.17)	3	60.00(7.23)	3	78.33(7.54)
	41	3	12.67(1.45)	3	17.30(2.01)	3	105.33(13.54)	3	62.00(15.95)	3	77.00(17.01)
	42	3	12.67(1.45)	3	17.57(1.87)	3	108.67(8.88)	3	70.33(17.29)	3	83.67(15.86)
	43	3	12.67(1.45)	3	17.70(1.56)	3	103.00(12.50)	3	59.00(17.44)	3	73.00(16.46)
	44	3	12.67(1.45)	3	17.03(2.02)	3	106.67(7.88)	3	66.33(16.18)	3	79.33(14.40)
	45	3	12.67(1.45)	3	17.17(2.19)	3	92.67(6.36)	3	56.33(13.57)	3	67.67(12.41)

Table 4b. Descriptive Statistics for Pulse Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Study Time Course in Air Control and CG-Exposed Groups (Continued)

Group	Study Time Course	Respiratory Rate (Breaths/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)1	N	Mean (SE)[1]
Control	46	3	12.67(1.45)	3	17.13(2.03)	3	104.33(6.77)	3	69.67(18.89)	3	81.33(15.21)
	47	3	12.67(1.45)	3	17.40(1.75)	3	104.33(11.26)	3	59.67(14.52)	3	74.00(15.00)
	48	3	12.67(1.45)	3	17.20(2.15)	3	92.67(6.84)	3	60.67(15.86)	3	72.00(15.39)
	49	3	12.67(1.45)	3	17.07(2.09)	3	99.00(7.51)	3	70.67(19.01)	3	79.00(16.92)
	50	2	12.50(2.50)	2	17.00(3.10)	2	150.00(30.00)	2	127.50(36.50)	2	95.50(7.50)
	51	3	12.67(1.45)	2	19.55(0.45)	3	132.33(25.26)	3	99.00(38.16)	3	109.67(34.98)
	52	3	12.67(1.45)	2	18.75(0.45)	3	130.33(21.48)	3	88.67(35.97)	3	102.67(31.06)
	53	3	12.67(1.45)	2	18.30(0.10)	3	126.33(19.60)	3	84.00(33.83)	3	96.33(30.82)
	54	3	12.67(1.45)	2	18.40(0.00)	3	122.33(16.41)	3	80.67(29.68)	3	93.67(25.47)
	55	3	12.67(1.45)	2	18.95(0.35)	3	119.33(15.92)	3	79.33(28.85)	3	92.67(24.70)
	56	3	12.67(1.45)	2	19.23(0.58)	3	105.67(11.46)	3	73.83(19.86)	3	85.83(17.65)
	57	3	12.67(1.45)	2	18.85(0.45)	3	111.33(8.41)	3	66.33(12.17)	3	82.33(12.17)
	58	2	12.50(2.50)	1	18.50(NA)	2	116.00(4.00)	2	68.00(2.00)	2	86.50(3.50)
	59	1	10.00(NA)	1	18.85(NA)	1	117.50(NA)	1	71.00(NA)	1	88.50(NA)
	60	3	12.67(1.45)	2	19.25(0.45)	3	115.67(2.73)	3	65.67(6.94)	3	84.33(6.06)
	61	3	12.67(1.45)	2	19.15(0.65)	3	102.67(7.42)	3	53.00(10.02)	3	70.33(10.67)
	62	3	12.67(1.45)	2	18.50(0.20)	3	106.67(7.45)	3	56.33(11.85)	3	73.33(11.46)
	63	3	12.67(1.45)	2	19.10(0.10)	3	105.00(5.03)	3	58.33(5.21)	3	76.00(5.13)
	64	3	12.67(1.45)	2	19.45(0.45)	3	104.00(4.93)	3	54.67(6.89)	3	72.67(7.54)
	65	3	12.67(1.45)	2	19.10(0.50)	3	103.67(1.20)	3	56.00(1.53)	3	74.00(1.53)
	66	3	12.67(1.45)	2	18.70(0.10)	3	99.00(2.08)	3	52.33(7.84)	3	67.33(3.84)
	67	3	12.67(1.45)	2	19.30(0.50)	3	97.00(1.73)	3	48.67(6.23)	3	64.00(4.51)
	68	3	12.67(1.45)	2	18.95(0.55)	3	107.00(4.62)	3	58.67(11.41)	3	77.33(11.67)
	69	3	12.67(1.45)	2	18.90(0.30)	3	102.00(2.52)	3	61.67(16.05)	3	74.67(11.41)
	70	2	14.00(1.00)	1	18.50(NA)	2	102.00(5.00)	2	46.00(7.00)	2	64.50(8.50)
	71	1	13.00(NA)	1	18.60(NA)	1	98.00(NA)	1	39.00(NA)	1	56.00(NA)
	72	1	13.00(NA)	1	18.70(NA)	1	99.00(NA)	1	41.00(NA)	1	59.00(NA)
Low	0	2	12.00(0.00)	0	NA (NA)	1	110.00(NA)	1	77.00(NA)	1	93.00(NA)
	1	2	12.00(0.00)	2	16.60(2.70)	2	117.50(0.50)	2	75.50(7.50)	2	93.00(7.00)
	2	2	12.00(2.00)	2	18.15(2.35)	2	115.00(8.00)	2	81.00(14.00)	2	94.50(7.50)
	3	2	14.00(2.00)	2	19.35(0.25)	2	122.50(3.50)	2	74.00(3.00)	2	93.00(1.00)
	4	2	14.00(2.00)	2	19.70(0.70)	2	113.50(1.50)	2	66.00(2.00)	2	84.00(1.00)
	5	2	14.50(2.50)	2	18.85(0.55)	2	111.00(1.00)	2	62.50(1.50)	2	80.00(2.00)
	6	2	14.00(2.00)	2	18.60(0.40)	2	135.00(24.00)	2	87.00(24.00)	2	105.00(26.00)
	7	2	15.50(0.50)	2	18.65(0.45)	2	131.00(15.00)	2	94.00(29.00)	2	121.00(39.00)
	8	2	17.50(2.50)	2	18.55(0.35)	2	130.00(4.00)	2	80.00(7.00)	1	93.00(NA)
	9	2	17.50(2.50)	2	18.65(0.25)	2	123.00(3.00)	2	71.00(4.00)	1	92.00(NA)
	10	2	16.00(1.00)	2	19.25(0.25)	2	83.00(7.00)	2	57.00(6.00)	2	66.00(2.00)
	11	2	17.50(2.50)	2	19.35(0.45)	2	123.50(19.50)	2	79.00(16.00)	2	93.50(14.50)
	12	2	16.00(1.00)	2	19.45(0.25)	2	126.50(11.50)	2	73.50(1.50)	2	92.50(2.50)
	13	2	16.00(1.00)	2	20.00(0.00)	2	95.50(15.50)	2	65.50(7.50)	2	77.50(10.50)
	14	2	16.00(1.00)	2	20.10(0.00)	2	87.50(12.50)	2	63.50(6.50)	2	70.50(8.50)
	15	2	17.00(0.00)	2	19.40(0.80)	2	98.00(0.00)	2	68.00(13.00)	2	78.00(8.00)

Table 4b. Descriptive Statistics for Pulse Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Study Time Course in Air Control and CG-Exposed Groups (Continued)

Group	Study Time Course	Respiratory Rate (Breaths/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)1	N	Mean (SE)[1]
Low	16	2	16.00(1.00)	2	19.20(0.90)	2	79.00(9.00)	2	53.50(3.50)	2	62.50(0.50)
	17	2	15.00(2.00)	2	19.60(0.60)	2	84.00(8.00)	2	55.00(4.00)	2	65.00(1.00)
	18	2	15.00(2.00)	2	19.45(0.45)	2	86.00(9.00)	2	56.00(1.00)	2	66.00(3.00)
	19	2	15.00(2.00)	2	19.15(1.15)	2	114.00(7.00)	2	81.50(0.50)	2	93.50(3.50)
	20	2	15.00(2.00)	2	18.45(0.95)	2	88.50(3.50)	2	70.00(15.00)	2	76.00(11.00)
	21	2	15.00(2.00)	2	18.50(0.50)	2	99.00(6.00)	2	90.50(2.50)	2	96.00(3.00)
	22	2	15.00(2.00)	2	18.40(0.20)	2	93.50(10.50)	2	70.50(4.50)	2	77.50(0.50)
	23	2	15.00(2.00)	2	18.60(0.80)	2	107.00(4.00)	2	67.50(2.50)	2	83.00(3.00)
	24	2	15.00(2.00)	2	18.60(1.00)	2	101.00(11.00)	2	77.00(8.00)	2	84.50(0.50)
	25	2	15.00(2.00)	2	18.35(0.45)	2	86.00(6.00)	2	59.50(17.50)	2	69.00(15.00)
	26	2	15.00(2.00)	2	18.25(0.35)	2	96.50(3.50)	2	72.50(6.50)	2	81.50(4.50)
	27	2	15.00(2.00)	2	17.85(0.85)	2	114.00(4.00)	2	69.00(3.00)	2	84.00(3.00)
	28	2	15.00(2.00)	2	17.90(0.80)	2	112.00(11.00)	2	73.50(0.50)	2	87.00(3.00)
	29	2	15.00(2.00)	2	17.25(0.15)	2	107.00(3.00)	2	95.50(7.50)	2	100.00(5.00)
	30	2	15.00(2.00)	2	17.10(0.00)	2	103.00(12.00)	2	92.00(14.00)	2	95.00(12.00)
	31	2	15.00(2.00)	2	17.50(0.80)	2	109.00(1.00)	2	67.50(4.50)	2	82.00(3.00)
	32	2	15.00(2.00)	2	17.40(0.90)	2	118.50(5.50)	2	73.00(7.00)	2	89.00(6.00)
	33	2	14.50(2.50)	2	17.50(0.70)	2	120.50(2.50)	2	70.50(0.50)	2	86.50(0.50)
	34	2	15.00(2.00)	2	17.25(0.35)	2	115.00(7.00)	2	63.50(7.50)	2	83.50(4.50)
	35	2	15.00(2.00)	2	17.05(0.95)	2	117.50(7.50)	2	74.00(7.00)	2	89.00(6.00)
	36	2	15.00(2.00)	2	16.85(1.15)	2	118.00(7.00)	2	72.00(5.00)	2	88.00(4.00)
	37	2	15.00(2.00)	2	17.25(0.45)	2	117.00(10.00)	2	75.50(8.50)	2	89.50(3.50)
	38	2	15.00(2.00)	2	16.90(0.80)	2	118.00(15.00)	2	75.00(6.00)	2	89.50(0.50)
	39	2	15.00(2.00)	2	16.80(0.70)	2	107.00(14.00)	2	78.50(5.50)	2	110.50(23.50)
	40	2	15.00(2.00)	2	16.60(0.70)	2	113.50(3.50)	2	71.00(1.00)	2	85.50(0.50)
	41	2	15.00(2.00)	2	16.45(0.15)	2	109.50(0.50)	2	72.00(3.00)	2	84.50(1.50)
	42	2	15.50(1.50)	2	16.55(0.05)	2	103.00(5.00)	2	73.50(0.50)	2	83.50(1.50)
	43	2	11.50(1.50)	2	16.90(0.30)	2	110.50(2.50)	2	73.50(1.50)	2	87.00(1.00)
	44	2	11.50(1.50)	2	16.80(0.30)	1	97.00(NA)	1	59.00(NA)	1	73.00(NA)
	45	2	11.50(1.50)	2	16.75(0.15)	2	108.00(2.00)	2	75.00(1.00)	2	87.00(0.00)
	46	2	11.50(1.50)	2	17.05(0.45)	2	93.50(9.50)	2	64.00(2.00)	2	75.00(5.00)
	47	2	12.50(0.50)	2	17.40(0.50)	2	115.00(0.00)	2	76.50(5.50)	2	87.50(6.50)
	48	2	12.50(0.50)	2	17.25(0.65)	2	113.50(7.50)	2	82.50(4.50)	2	94.00(6.00)
	49	2	13.50(1.50)	2	17.80(0.30)	2	93.00(5.00)	2	71.00(1.00)	2	80.00(1.00)
	50	2	13.50(1.50)	2	17.25(0.85)	2	105.50(2.50)	2	74.00(2.00)	2	87.00(2.00)
	51	2	7.50(7.50)	2	17.50(0.20)	2	107.50(3.50)	2	74.50(7.50)	2	83.00(1.00)
	52	2	13.50(1.50)	2	17.65(0.45)	2	120.00(0.00)	2	77.00(6.00)	2	91.50(4.50)
	53	2	14.00(1.00)	2	17.20(1.20)	2	116.00(9.00)	2	75.50(11.50)	2	91.50(9.50)
	54	2	14.00(1.00)	2	17.15(1.25)	2	122.50(7.50)	2	84.50(11.50)	2	97.00(12.00)
	55	2	14.00(1.00)	2	17.60(0.70)	2	117.50(0.50)	2	78.00(4.00)	2	90.50(4.50)
	56	2	14.00(1.00)	2	17.75(0.75)	2	116.00(8.00)	2	67.50(1.50)	2	82.50(0.50)
	57	2	14.00(1.00)	2	17.90(1.40)	2	120.50(10.50)	2	81.00(24.00)	2	92.00(22.00)
	58	2	13.00(0.00)	2	18.00(1.60)	2	114.50(10.50)	2	76.00(13.00)	2	89.50(12.50)

Table 4b. Descriptive Statistics for Pulse Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Study Time Course in Air Control and CG-Exposed Groups (Continued)

Group	Study Time Course	Respiratory Rate (Breaths/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)1	N	Mean (SE)[1]
Low	59	2	13.00(0.00)	2	17.65(1.15)	2	105.00(9.00)	2	87.00(25.00)	2	96.00(21.00)
	60	2	13.00(0.00)	2	17.65(0.95)	2	100.00(7.00)	2	64.00(3.00)	2	77.50(4.50)
	61	2	13.00(0.00)	2	18.30(1.30)	2	101.00(5.00)	2	63.00(5.00)	2	80.50(1.50)
	62	2	13.00(0.00)	2	18.40(1.30)	2	93.00(13.00)	2	59.50(5.50)	2	71.50(8.50)
	63	2	13.00(0.00)	2	17.65(0.95)	2	99.50(17.50)	2	65.00(12.00)	2	76.00(14.00)
	64	2	13.00(0.00)	2	17.50(0.80)	2	96.00(2.00)	2	59.00(3.00)	2	72.00(1.00)
	65	2	13.00(0.00)	2	17.85(0.85)	2	105.00(20.00)	2	73.00(17.00)	2	83.50(18.50)
	66	2	13.00(0.00)	2	17.70(1.00)	2	107.50(10.50)	2	74.00(9.00)	2	86.00(10.00)
	67	2	13.00(0.00)	2	17.40(1.10)	2	117.50(4.50)	2	83.00(6.00)	2	95.00(5.00)
	68	2	13.00(0.00)	2	17.65(1.45)	2	84.50(14.50)	2	61.00(7.00)	2	87.50(8.50)
	69	2	13.00(0.00)	2	17.95(2.15)	1	111.00(NA)	1	83.00(NA)	1	92.00(NA)
	70	2	13.00(0.00)	2	18.20(2.40)	2	101.00(0.00)	2	69.50(8.50)	2	79.50(4.50)
	71	2	12.50(0.50)	2	18.90(2.10)	2	103.50(4.50)	2	74.50(7.50)	2	84.00(2.00)
	72	1	13.00(NA)	1	20.90(NA)	1	115.00(NA)	1	71.00(NA)	1	86.00(NA)
Medium	0	5	15.00(0.00)	2	19.95(4.05)	2	105.50(4.50)	2	59.00(5.00)	2	79.50(5.50)
	1	6	15.50(0.34)	6	20.91(1.74)	5	105.10(4.07)	5	60.90(6.29)	5	77.80(5.87)
	2	6	15.75(0.57)	6	21.17(1.58)	5	108.80(5.34)	5	58.00(4.97)	5	76.40(5.06)
	3	6	16.38(1.03)	6	21.28(1.60)	5	108.60(3.47)	5	58.60(2.18)	5	77.00(2.17)
	4	6	16.50(1.15)	6	20.33(1.36)	5	103.60(4.47)	5	53.60(2.79)	5	72.20(3.93)
	5	6	16.67(1.12)	6	20.20(1.32)	4	103.25(6.01)	4	57.00(4.14)	4	72.75(3.52)
	6	6	16.67(1.12)	6	20.52(1.34)	5	113.40(5.76)	5	72.80(6.11)	5	87.60(4.25)
	7	6	19.00(2.54)	6	20.72(1.34)	5	110.40(9.73)	5	67.40(11.76)	5	83.40(10.36)
	8	5	17.80(1.59)	5	21.54(1.19)	4	82.00(1.58)	4	63.00(4.78)	4	68.50(3.86)
	9	5	17.40(1.29)	5	21.44(1.14)	4	69.50(20.61)	4	35.75(10.18)	4	47.75(13.79)
	10	4	16.75(1.44)	4	21.60(1.68)	3	100.33(6.94)	3	51.67(3.76)	3	67.67(4.18)
	11	4	16.75(1.44)	4	21.28(1.13)	3	95.67(4.41)	3	47.33(2.73)	3	64.00(2.65)
	12	4	16.75(1.44)	4	20.93(1.00)	3	104.00(6.56)	3	48.00(2.52)	3	67.00(3.79)
	13	4	16.75(1.44)	4	20.98(1.38)	3	104.33(7.36)	3	52.67(5.36)	3	69.33(4.26)
	14	4	16.00(0.71)	4	21.25(1.50)	3	120.67(8.19)	3	66.67(4.37)	3	83.67(4.67)
	15	4	16.25(0.95)	4	21.28(1.30)	3	125.00(10.79)	3	71.00(1.00)	3	89.00(3.79)
	16	4	16.25(0.95)	4	21.33(1.29)	3	106.00(6.08)	3	62.00(2.08)	3	78.33(3.18)
	17	4	16.25(0.95)	4	21.00(1.27)	3	108.67(11.89)	3	71.33(2.96)	3	85.00(5.03)
	18	4	18.50(2.02)	4	21.28(1.47)	3	115.67(8.69)	3	66.67(1.86)	3	84.67(1.86)
	19	4	16.50(0.87)	4	21.28(1.40)	3	107.33(3.18)	3	72.67(5.55)	3	85.33(3.38)
	20	3	15.33(0.33)	3	20.83(2.05)	3	105.00(6.03)	3	70.67(10.84)	3	84.67(10.04)
	21	3	15.33(0.33)	3	20.77(1.78)	3	103.33(6.36)	3	64.00(11.24)	3	76.33(10.35)
	22	3	15.00(0.58)	3	21.67(2.43)	3	124.67(19.38)	3	75.00(13.32)	3	93.33(14.44)
	23	3	15.00(0.58)	3	21.50(2.19)	3	107.67(12.99)	3	69.67(15.43)	3	87.67(17.53)
	24	3	15.33(0.33)	3	21.23(1.99)	3	127.00(20.65)	3	72.00(14.73)	3	91.33(15.19)
	25	3	15.33(0.33)	3	20.47(1.67)	3	112.33(11.05)	3	63.33(9.13)	3	81.33(9.67)
	26	3	15.33(0.33)	3	20.47(1.89)	3	124.33(9.60)	3	72.33(9.17)	3	91.67(8.65)
	27	3	15.33(0.33)	3	20.57(1.59)	3	119.00(8.74)	3	70.33(6.67)	3	88.33(7.45)
	28	3	15.33(0.33)	3	20.93(2.05)	3	113.00(3.21)	3	63.33(5.46)	3	81.00(5.00)

Table 4b. Descriptive Statistics for Pulse Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Study Time Course in Air Control and CG-Exposed Groups (Continued)

Group	Study Time Course	Respiratory Rate (Breaths/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)1	N	Mean (SE)[1]
Medium	29	3	15.33(0.33)	3	20.73(1.99)	3	119.67(12.33)	3	74.67(7.84)	3	93.00(7.55)
	30	3	15.33(0.33)	3	20.60(1.86)	3	117.00(16.56)	3	71.67(8.88)	3	87.00(9.87)
	31	3	15.33(0.33)	3	20.37(2.02)	3	116.33(15.34)	3	72.00(9.54)	3	87.33(9.53)
	32	3	15.33(0.33)	3	20.20(1.93)	3	121.67(9.13)	3	76.67(5.21)	3	92.00(3.61)
	33	3	15.33(0.33)	3	20.07(2.03)	3	123.00(5.13)	3	72.33(1.45)	3	90.67(3.67)
	34	3	15.33(0.33)	3	20.70(2.30)	3	112.67(3.28)	3	63.33(2.73)	3	81.67(2.85)
	35	3	15.33(0.33)	3	21.00(2.10)	3	117.33(4.06)	3	76.00(7.81)	3	91.33(5.78)
	36	3	15.33(0.33)	3	20.73(2.03)	3	115.67(7.17)	3	68.00(6.66)	3	86.33(6.01)
	37	3	14.00(1.00)	3	20.63(2.07)	3	106.67(0.88)	3	59.67(2.67)	3	76.67(2.19)
	38	3	14.00(1.00)	3	21.00(2.42)	3	112.33(6.57)	3	69.67(5.33)	3	86.00(4.62)
	39	3	14.00(1.00)	3	20.93(2.44)	3	92.33(7.97)	3	63.33(5.84)	3	74.67(2.96)
	40	2	13.50(1.50)	2	18.80(1.60)	2	101.00(9.00)	2	65.50(6.50)	2	79.50(2.50)
	41	3	14.00(1.00)	3	20.38(2.24)	2	105.00(9.00)	2	81.00(8.00)	2	91.00(8.00)
	42	3	14.00(1.00)	3	21.03(2.58)	2	104.00(4.00)	2	67.50(8.50)	2	80.50(4.50)
	43	3	14.00(1.00)	3	21.03(2.53)	2	99.50(3.50)	2	68.50(12.50)	2	80.00(7.00)
	44	3	14.00(1.00)	3	20.67(2.29)	2	106.50(6.50)	2	86.00(7.00)	2	94.50(7.50)
	45	3	14.67(0.33)	3	20.63(2.23)	2	96.50(3.50)	2	66.00(9.00)	2	78.00(4.00)
	46	3	14.67(0.33)	3	20.80(2.65)	2	96.00(3.00)	2	66.50(12.50)	2	78.00(7.00)
	47	3	14.67(0.33)	3	20.77(2.40)	2	100.00(2.00)	2	71.00(18.00)	2	82.00(13.00)
	48	3	14.67(0.33)	3	20.27(2.23)	2	103.50(9.50)	2	74.00(2.00)	2	85.00(4.00)
	49	3	14.67(0.33)	3	19.93(2.12)	2	105.50(0.50)	2	61.50(6.50)	2	78.50(4.50)
	50	3	14.67(0.33)	3	20.33(2.61)	2	95.50(1.50)	2	69.00(10.00)	2	80.00(6.00)
	51	3	14.67(0.33)	3	20.47(2.48)	2	94.00(16.00)	2	62.50(7.50)	2	75.50(10.50)
	52	3	15.67(0.67)	3	20.70(2.55)	2	113.00(4.00)	2	79.00(19.00)	2	92.00(13.00)
	53	3	14.67(0.33)	3	20.33(2.12)	2	105.00(2.00)	2	72.00(15.00)	2	85.00(9.00)
	54	3	14.67(0.33)	3	20.27(2.00)	2	100.50(0.50)	2	67.00(17.00)	2	80.00(10.00)
	55	3	14.67(0.33)	3	20.13(2.03)	2	106.00(1.00)	2	76.00(18.00)	2	87.00(11.00)
	56	3	14.67(0.33)	3	20.33(2.01)	2	99.00(1.00)	2	67.50(19.50)	2	81.50(10.50)
	57	3	14.67(0.33)	3	19.53(2.05)	2	101.50(1.50)	2	66.50(15.50)	2	78.50(8.50)
	58	3	14.67(0.33)	3	19.90(2.32)	2	101.50(0.50)	2	66.50(16.50)	2	80.50(10.50)
	59	3	14.00(1.00)	2	22.20(1.40)	2	101.50(2.50)	2	67.00(23.00)	2	78.50(16.50)
	60	3	14.00(1.00)	3	20.43(2.60)	2	100.50(0.50)	2	68.00(19.00)	2	80.50(12.50)
	61	3	14.00(1.00)	3	20.30(2.66)	2	99.00(3.00)	2	64.00(13.00)	2	77.00(7.00)
	62	3	14.00(1.00)	3	20.50(2.79)	2	101.50(1.50)	2	65.50(16.50)	2	79.50(10.50)
	63	3	14.00(1.00)	3	20.73(2.54)	2	102.50(6.50)	2	69.00(11.00)	2	83.00(3.00)
	64	3	14.00(1.00)	3	20.37(2.22)	2	91.50(0.50)	2	58.50(18.50)	2	70.00(12.00)
	65	3	14.00(1.00)	3	20.13(2.41)	2	90.00(7.00)	2	51.00(5.00)	2	64.50(0.50)
	66	3	14.00(1.00)	3	20.80(3.01)	2	98.50(1.50)	2	55.00(9.00)	2	71.00(5.00)
	67	3	14.00(1.00)	3	20.20(2.72)	2	104.00(7.00)	2	58.00(11.00)	2	75.00(9.00)
	68	3	14.00(1.00)	3	19.97(2.50)	2	103.00(7.00)	2	59.50(14.50)	2	76.00(12.00)
	69	3	14.00(1.00)	3	19.77(2.35)	2	89.50(2.50)	2	58.50(16.50)	2	71.00(10.00)
	70	3	14.00(1.00)	3	20.40(2.50)	2	77.00(24.00)	2	47.00(2.00)	2	58.50(10.50)
	71	3	14.00(1.00)	3	20.30(2.14)	2	83.50(20.50)	2	53.00(2.00)	2	64.50(6.50)
	72	1	12.00(NA)	1	16.60(NA)	1	93.00(NA)	1	82.00(NA)	1	87.00(NA)

Table 4b. Descriptive Statistics for Pulse Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Study Time Course in Air Control and CG-Exposed Groups (Continued)

Group	Study Time Course	Respiratory Rate (Breaths/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)[1]	N	Mean (SE)1	N	Mean (SE)[1]
High	0	3	14.00(1.00)	0	NA (NA)	1	98.00(NA)	1	60.00(NA)	1	78.00(NA)
	1	3	14.00(1.00)	3	21.26(1.24)	3	92.67(4.81)	3	57.33(3.38)	3	72.00(2.08)
	2	3	15.33(0.33)	3	22.05(1.81)	3	86.33(5.24)	3	50.00(3.46)	3	65.00(1.53)
	3	3	15.50(0.50)	3	21.05(0.90)	3	84.00(6.81)	3	58.33(2.85)	3	68.00(2.52)
	4	3	15.67(0.67)	3	20.70(0.95)	3	100.00(16.86)	3	63.00(6.66)	3	75.67(9.13)
	5	3	15.67(1.20)	3	19.73(0.68)	3	107.67(4.26)	3	89.67(13.98)	3	94.67(10.73)
	6	2	16.50(1.50)	2	20.25(1.05)	2	66.00(56.00)	2	61.50(60.50)	2	64.00(58.00)
	7	1	15.00(NA)	1	21.10(NA)	1	56.00(NA)	1	41.00(NA)	1	46.00(NA)
	8	1	15.00(NA)	1	20.80(NA)	1	79.00(NA)	1	58.00(NA)	1	65.00(NA)
	9	0	NA (NA)	1	21.80(NA)	1	15.00(NA)	1	15.00(NA)	1	15.00(NA)
Death		5	17.40(1.03)	6	19.83(0.80)	5	53.00(25.89)	5	31.00(14.73)	5	39.60(18.92)

[1] SE=Standard Error

Table 5. Summary Statistics for Wet to Dry Lung Weight Ratio in Air Control and CG-Exposed Groups.

Animals	Side of the Animal	N	Mean	Standard Deviation	Minimum	Maximum
Air Control	Upside	2	6.53	0.38	6.27	6.80
	Downside	2	6.51	0.02	6.50	6.53
CG-Exposed (Lived)	Upside	3	6.18	0.43	5.80	6.65
	Downside	3	6.46	0.47	5.93	6.80
CG-Exposed (Died)	Upside	4	8.40	0.65	7.80	9.27
	Downside	4	8.48	1.80	6.13	10.48

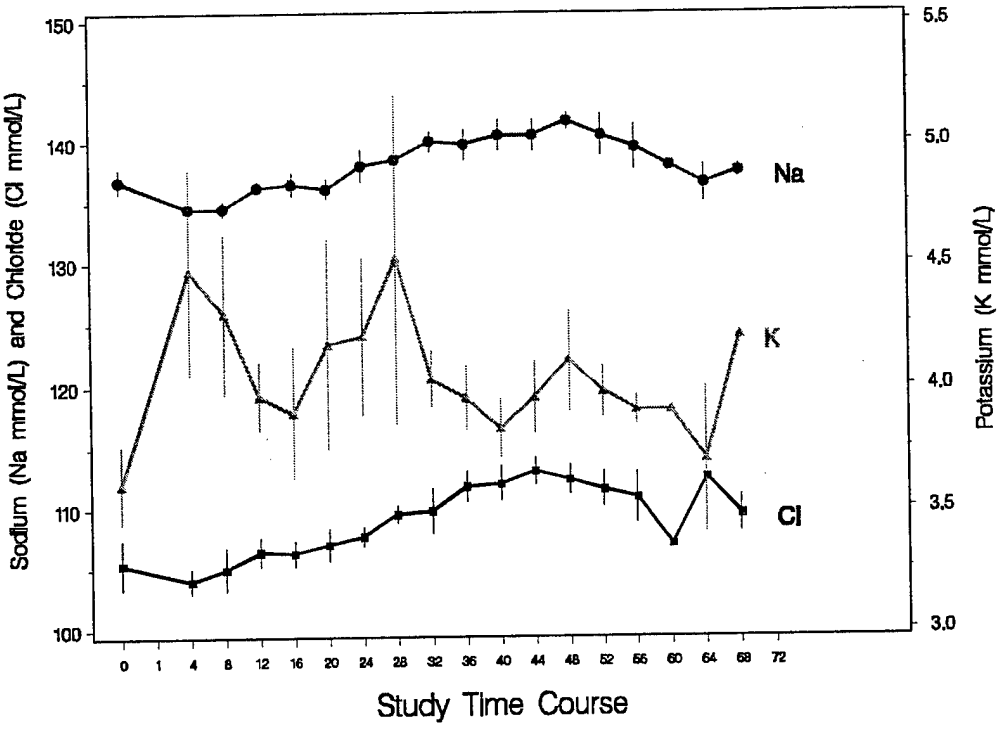

Figure 1a. **Sodium (Na), Chloride (Cl), and Potassium (K) Values in Anesthetized Group**

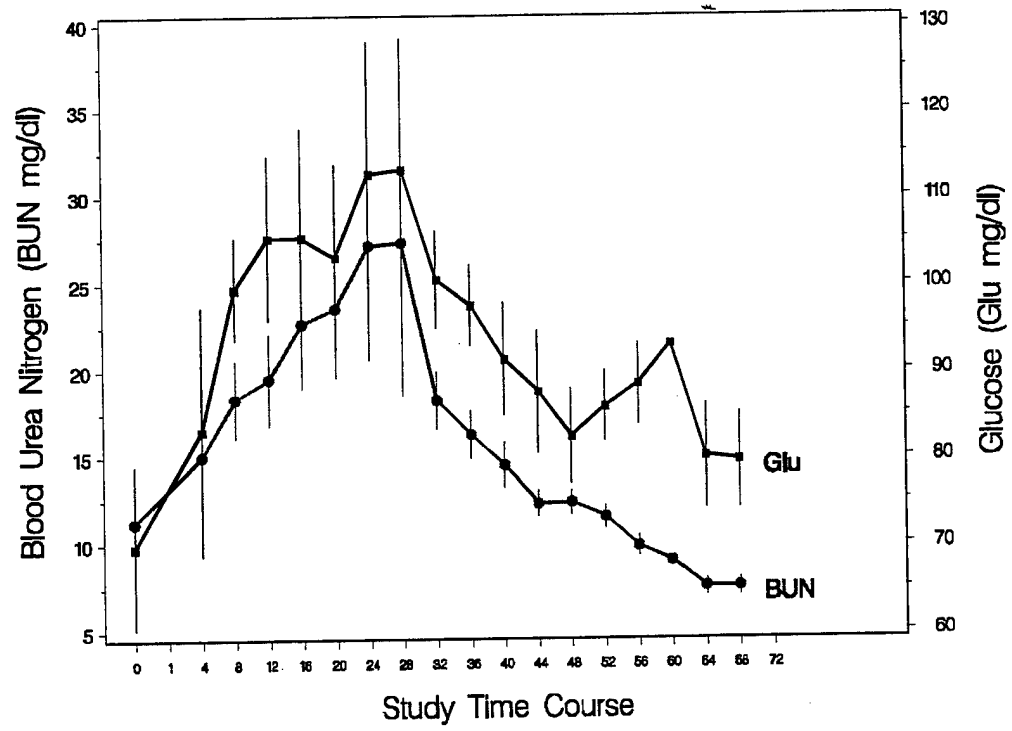

Figure 1b. **Blood Urea Nitrogen (BUN) and Blood Glucose (Glu) Values in Anesthetized Group**

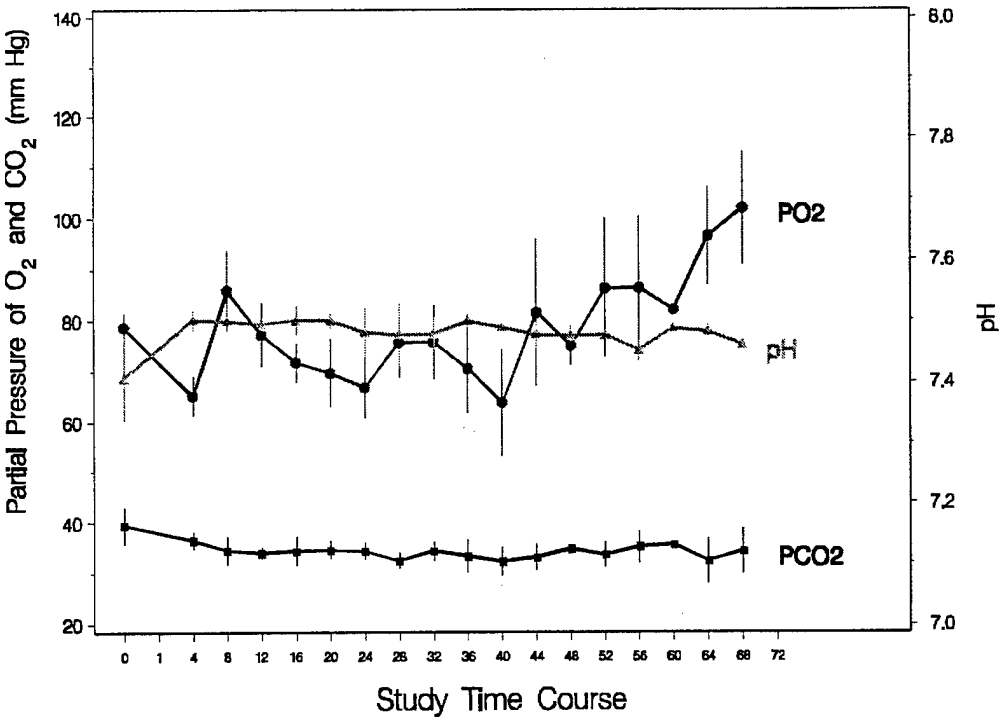

Figure 1c. **Arterial Partial Pressure of Oxygen (PO2), Arterial Partial Pressure of CO_2 (PCO2), and pH Values in Anesthetized Group**

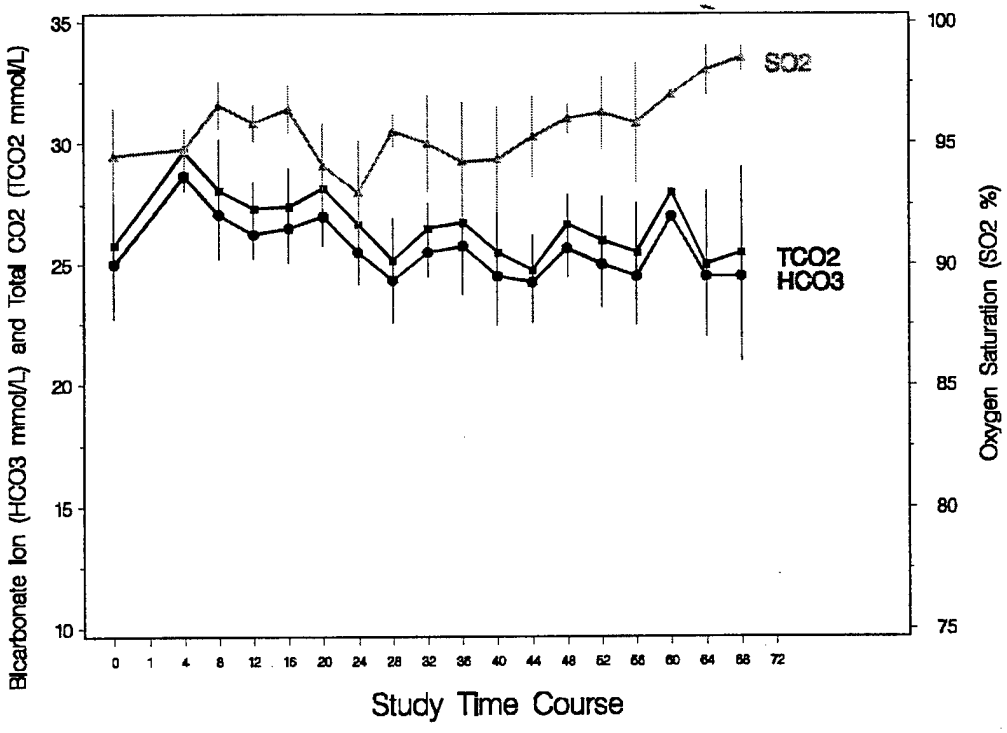

Figure 1d. **Bicarbonate Ion (HCO3), Total CO_2 (TCO2), and Oxygen Saturation (SO2) Values in Anesthetized Group**

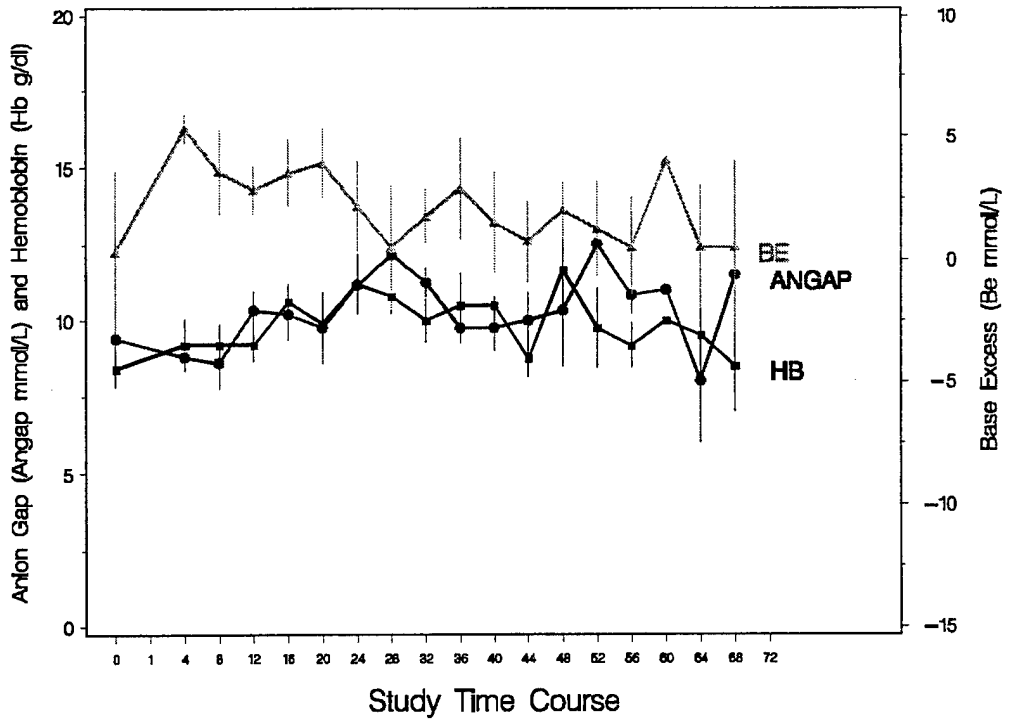

Figure 1e. **Anion Gap (ANGAP), Hemoglobin (HB), and Base Excess (BE) Values in Anesthetized Group**

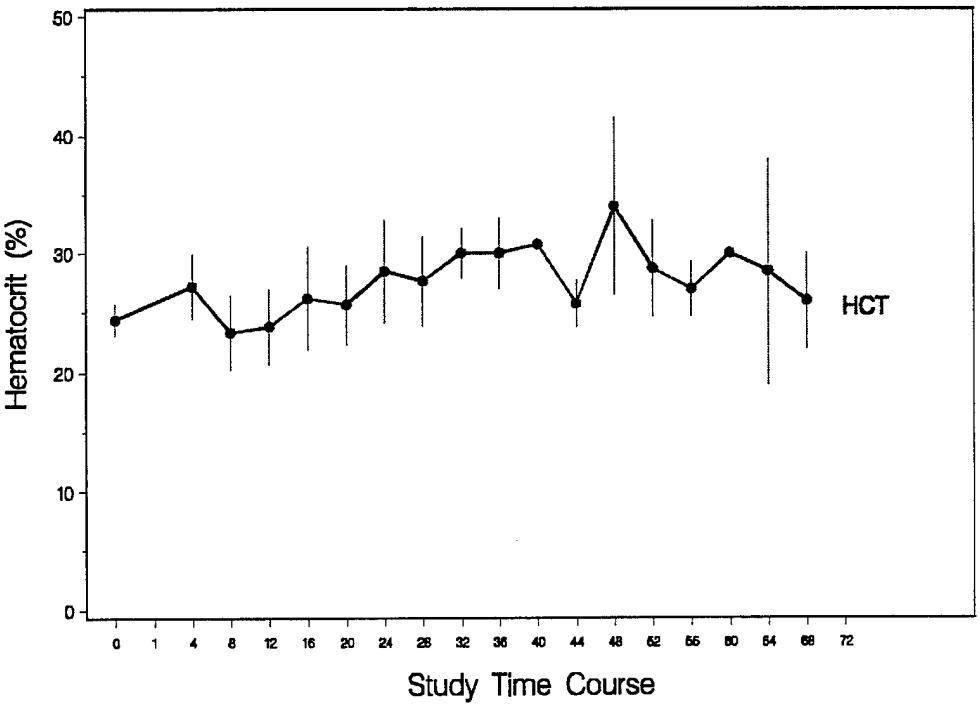

Figure 1f. **Hematocrit (HCT) Values in Anesthetized Group**

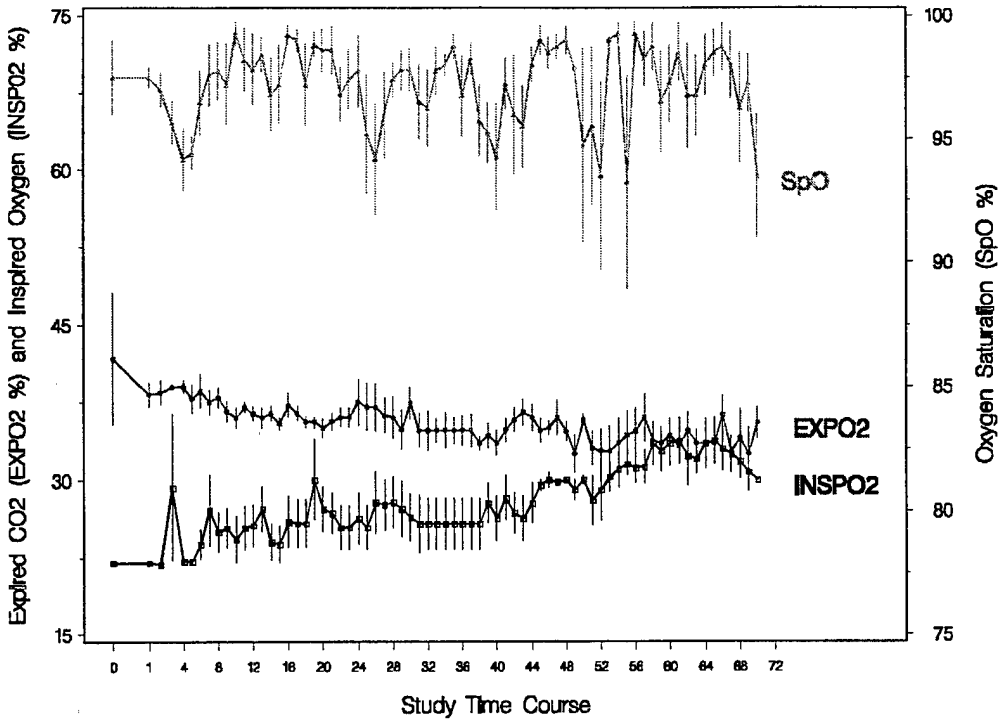

Figure 2a. **Expired CO_2 (EXPO2), Inspired CO_2 (INSPO2), and Oxygen Saturation (SpO) Values in Anesthetized Group**

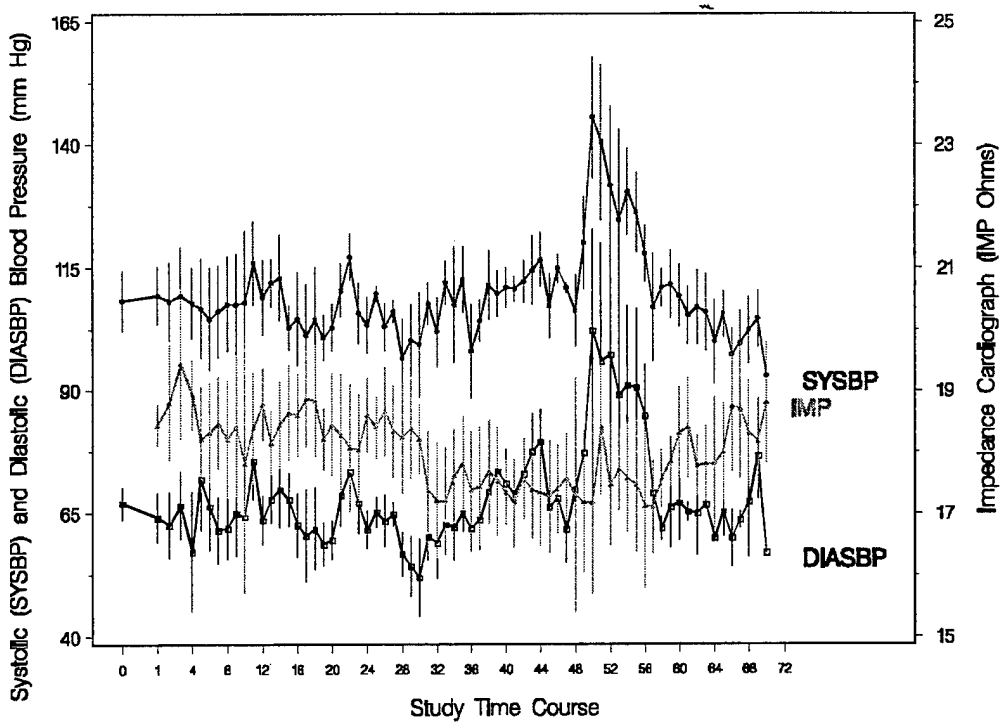

Figure 2b. **Systolic Blood Pressure (SYSBP), Diastolic Blood Pressure (DIASBP), and Impedance Cardiograph (IMP) Values in Anesthetized Group**

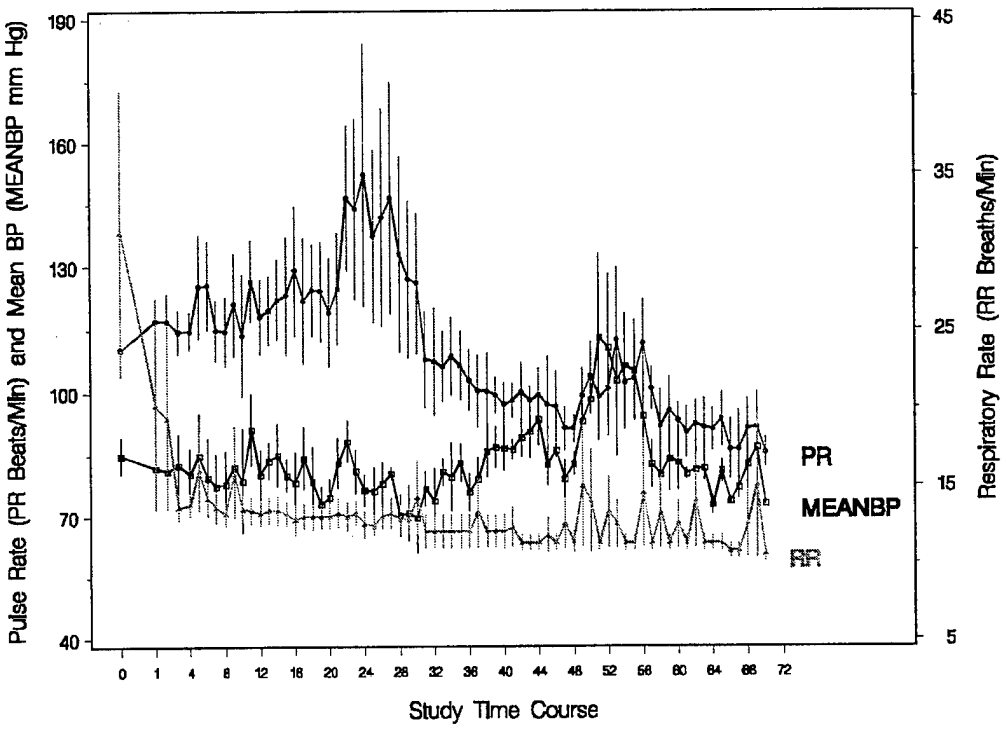

Figure 2c. **Pulse Rate (PR), Mean Blood Pressure (MEANBP), and Respiratory Rate (RR) Values in Anesthetized Group**

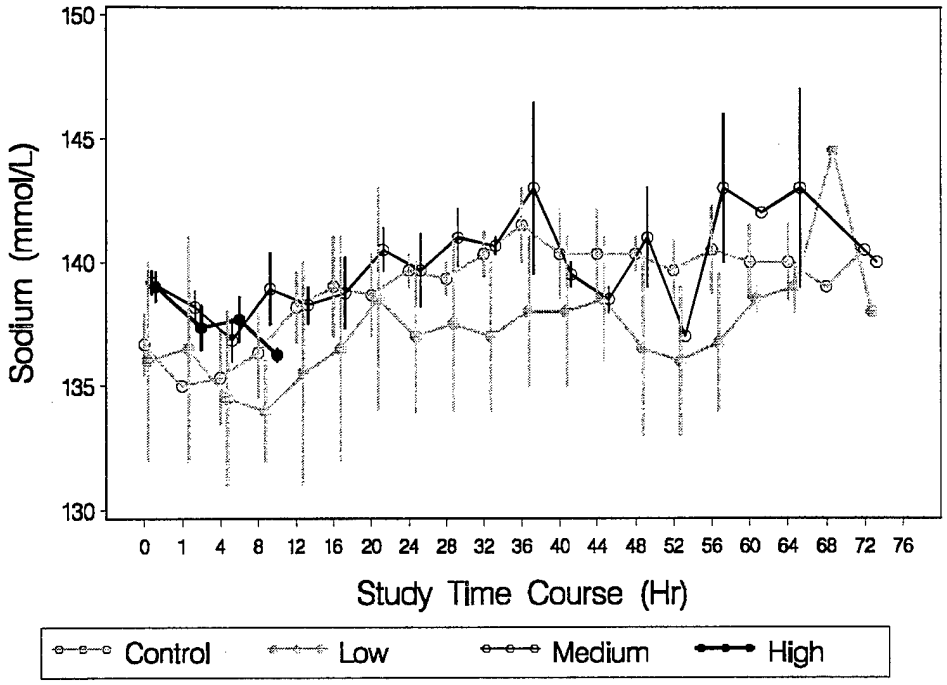

Figure 3a. Sodium Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

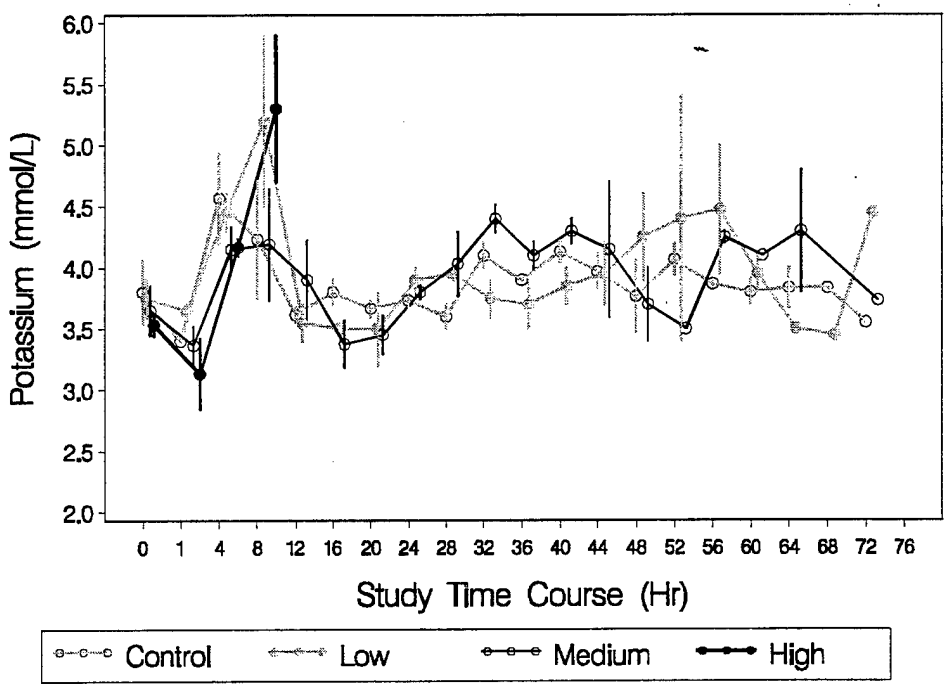

Figure 3b. Potassium in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

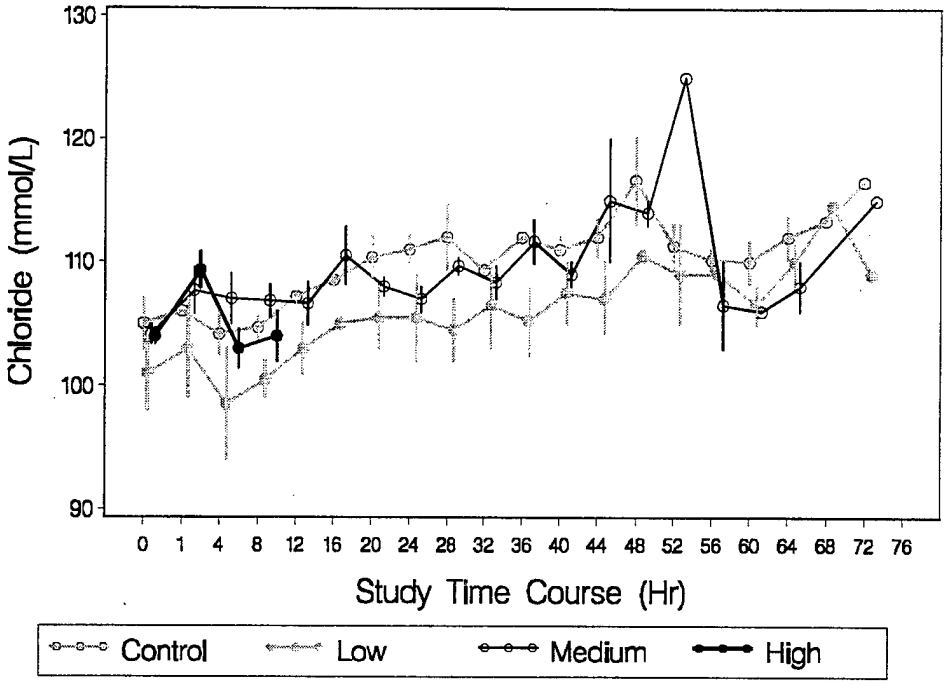

Figure 3c. Chloride Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

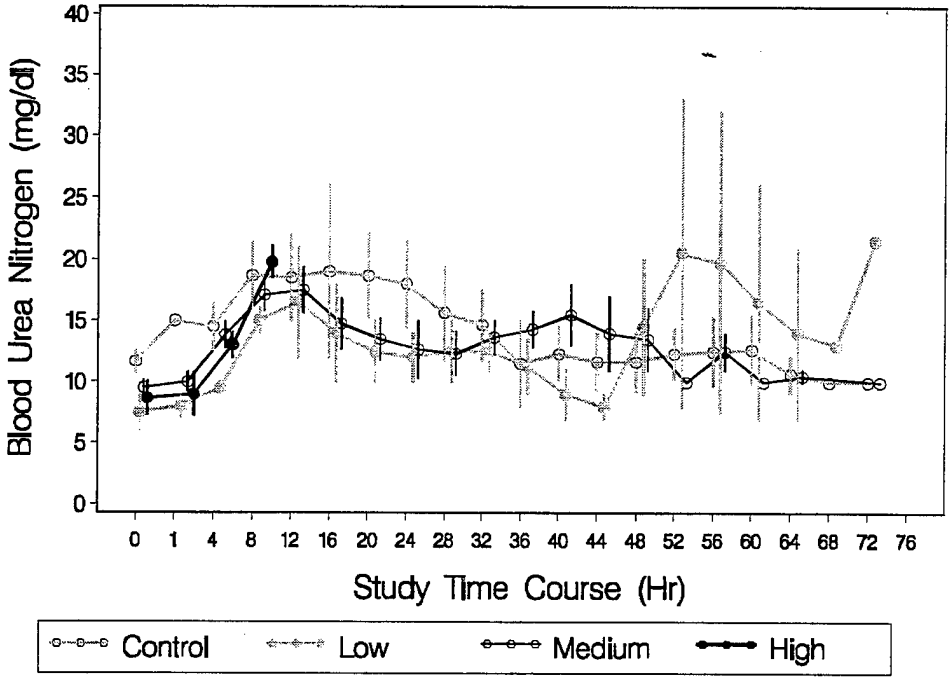

Figure 3d. Blood Urea Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

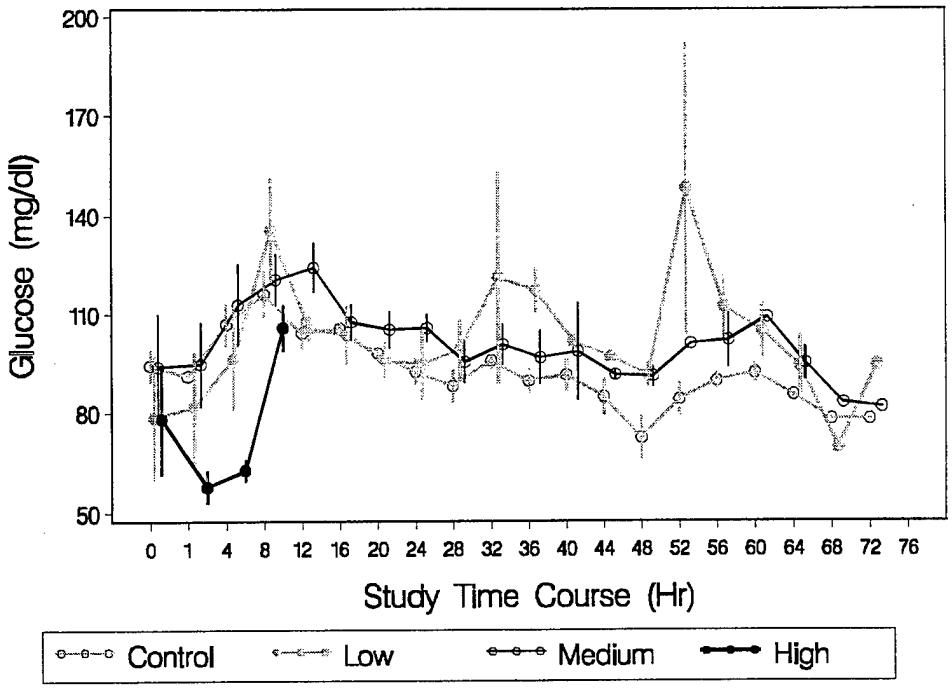

Figure 3e. **Blood Glucose Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups**

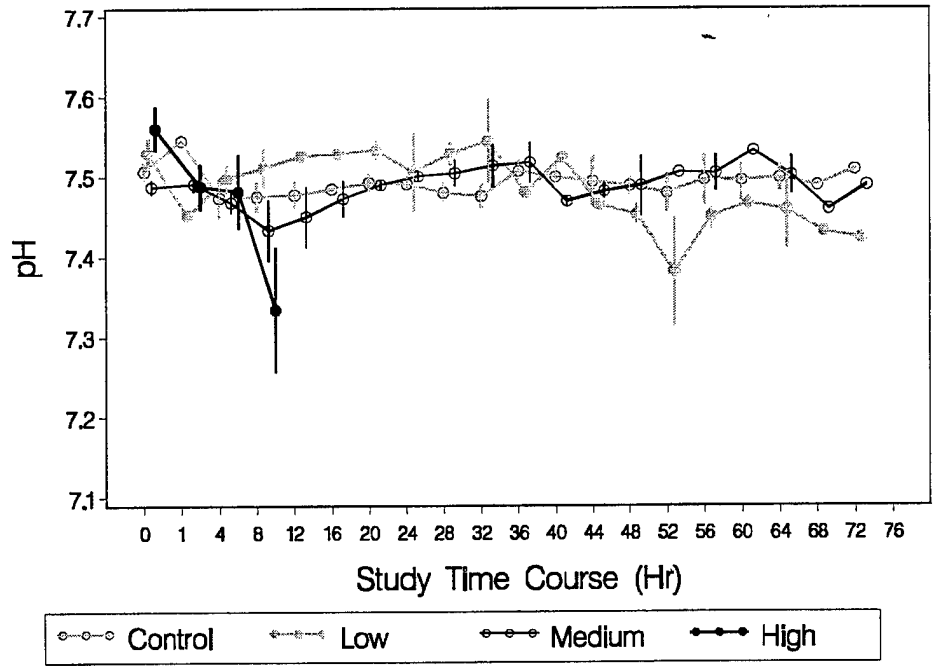

Figure 3f. **Arterial pH Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups**

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

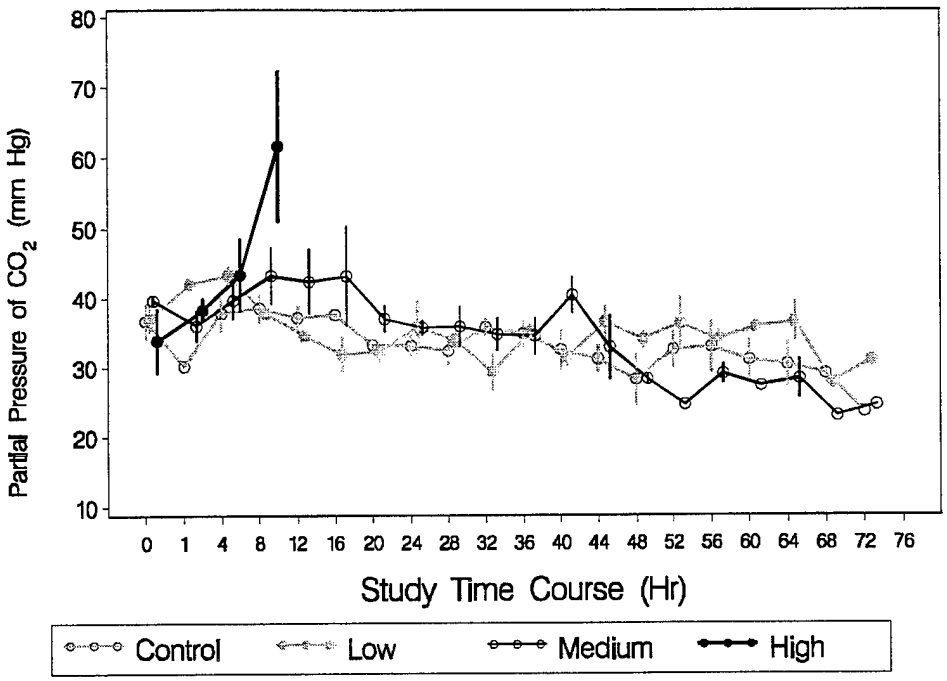

Figure 3g. **Arterial Partial Pressure of CO_2 Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups**

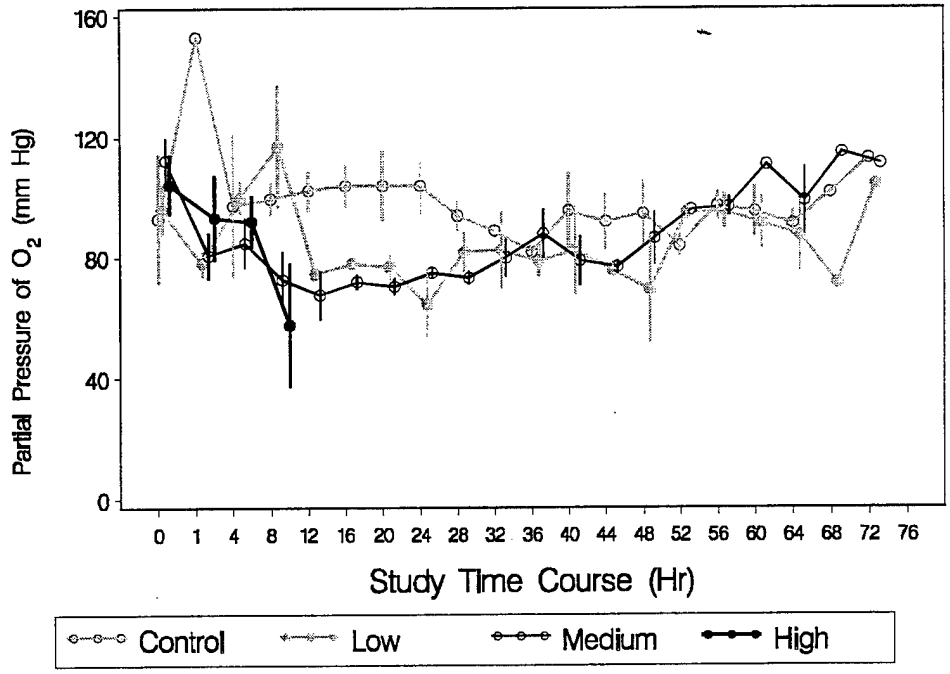

Figure 3h. **Arterial Partial Pressure of O_2 Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups**

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

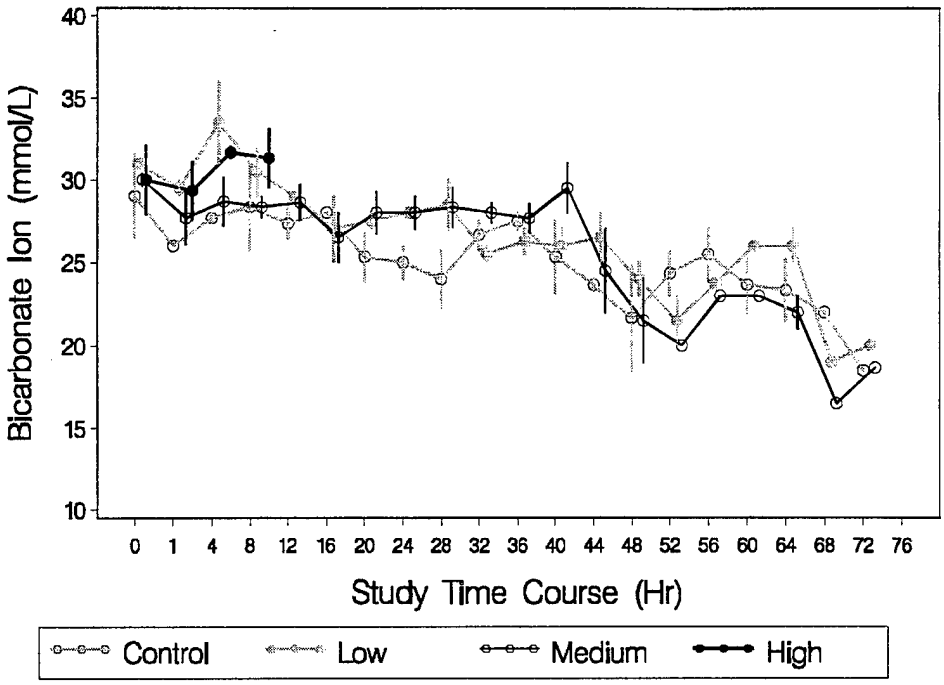

Figure 3i. Bicarbonate Ion Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

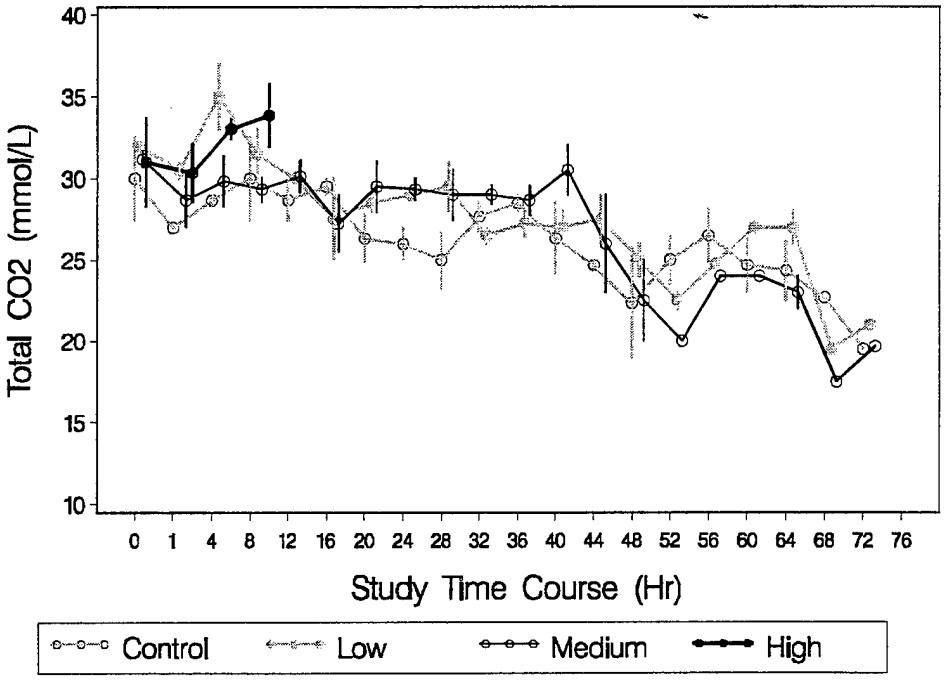

Figure 3j. Total CO_2 Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

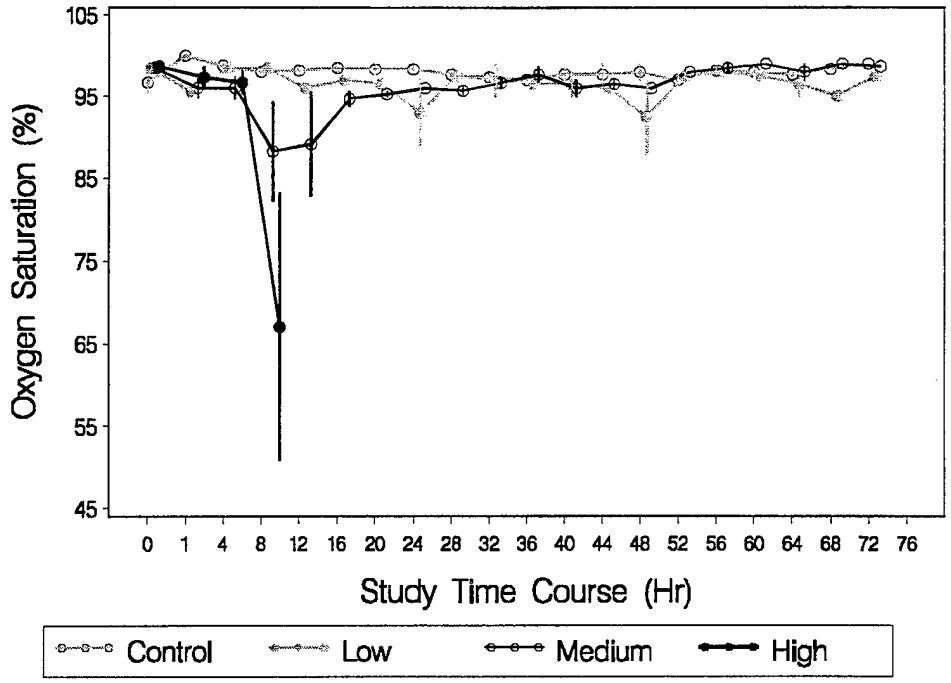

Figure 3k. **Oxygen Saturation Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups**

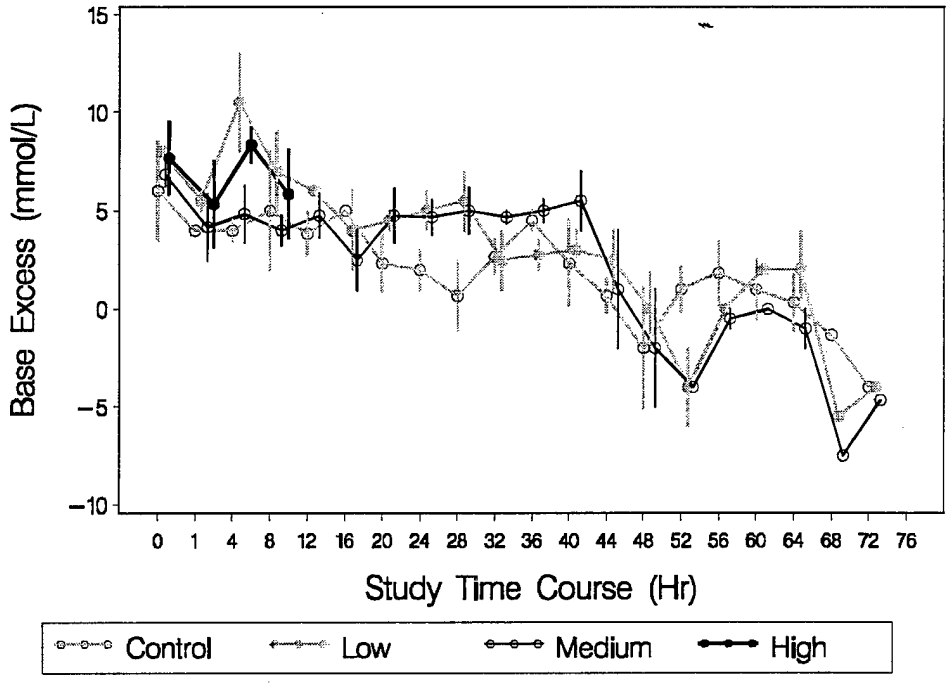

Figure 3l. **Base Excess Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups**

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

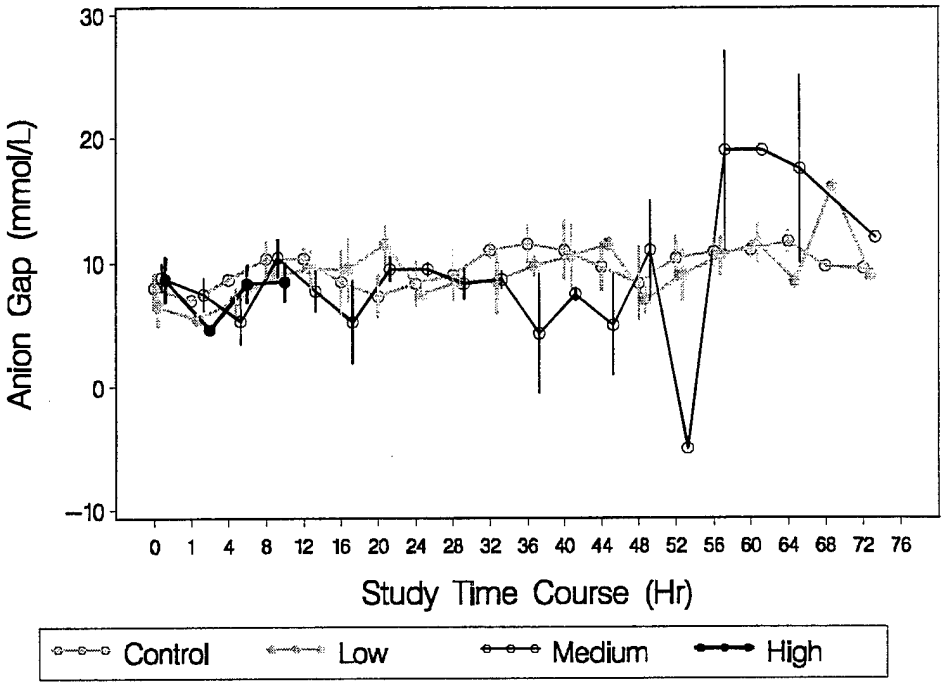

Figure 3m. Anion Gap Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

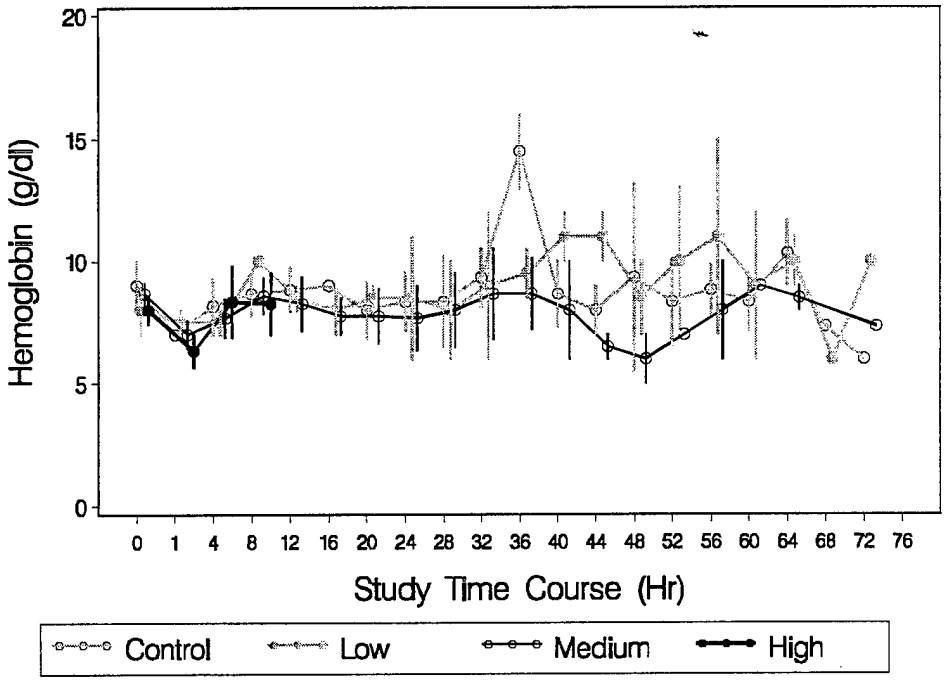

Figure 3n. Hemoglobin Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

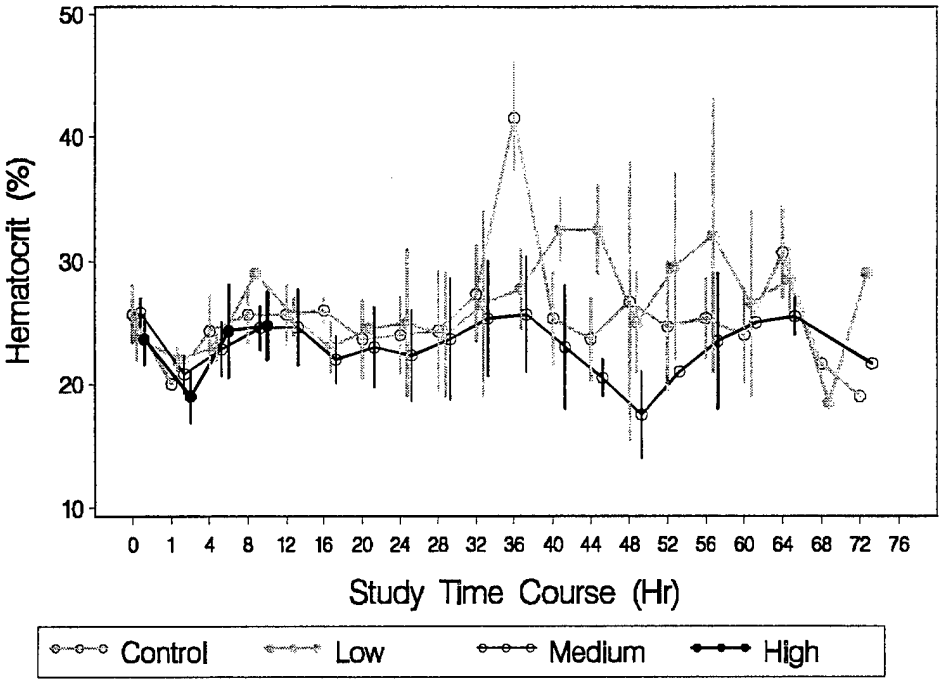

Figure 3o. Hematocrit Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

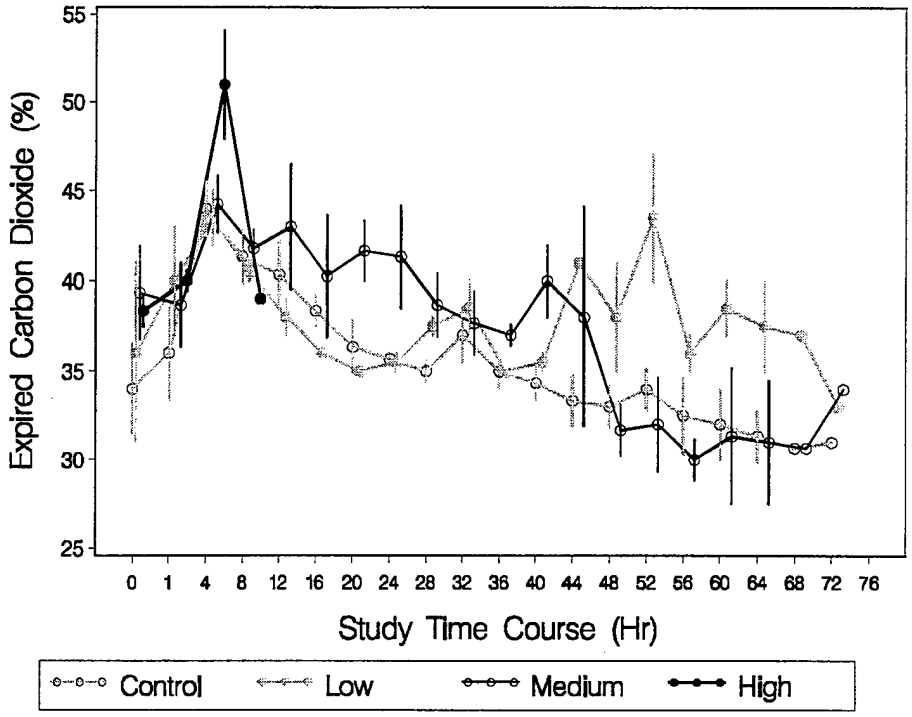

Figure 4a. Expired Carbon Dioxide Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

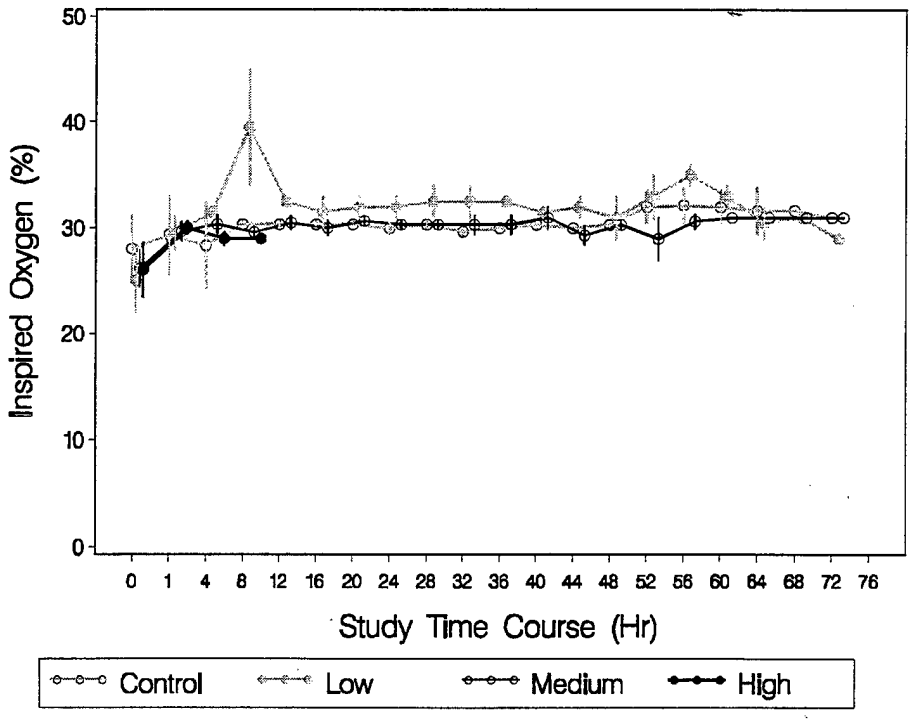

Figure 4b. Inspired Oxygen Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

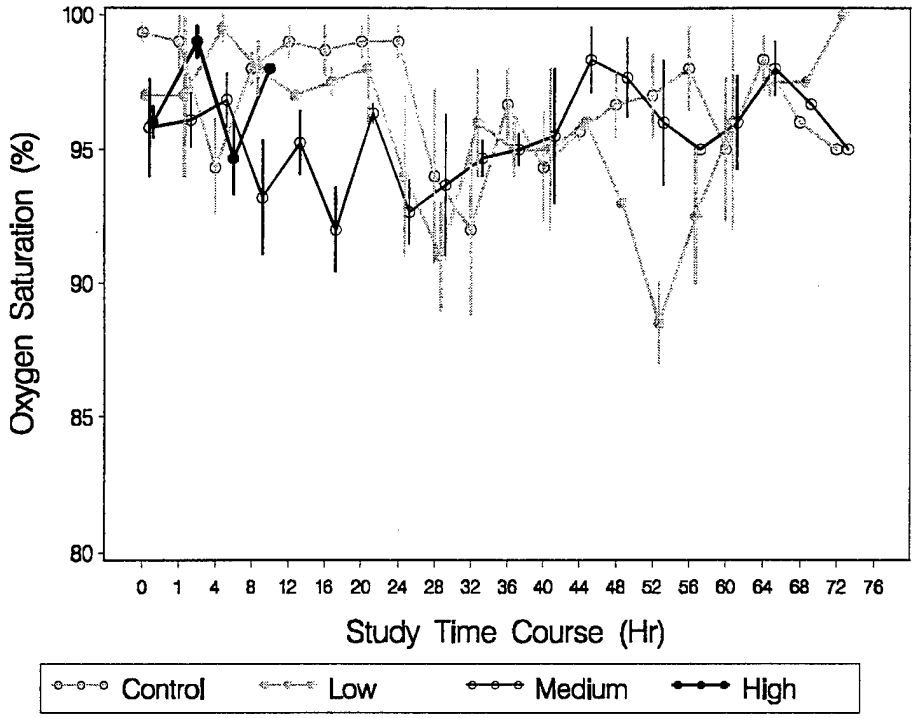

Figure 4c. Oxygen Saturation Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

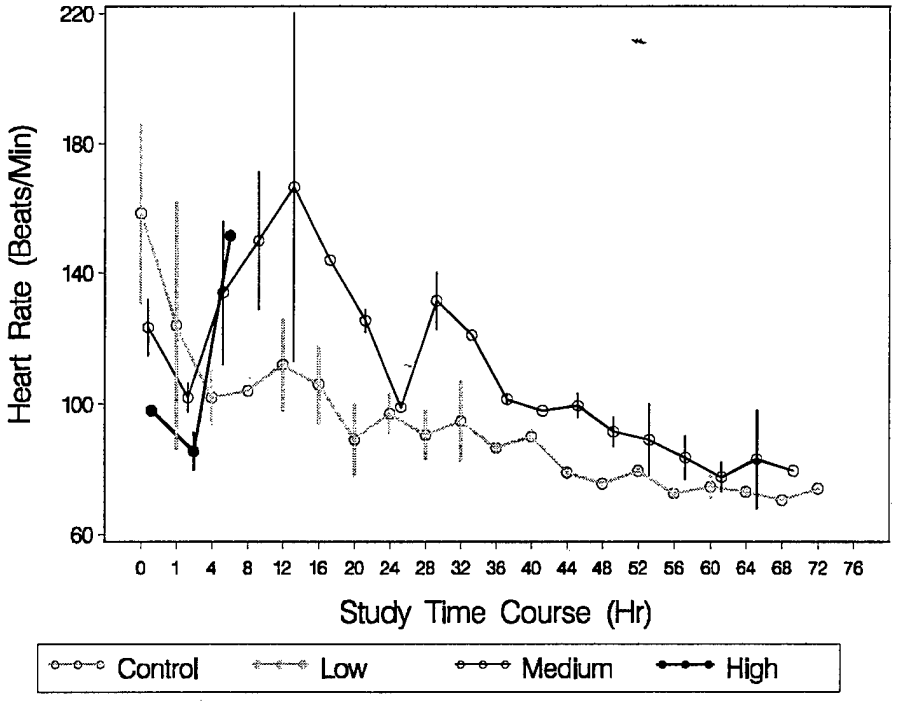

Figure 4d. Heart Rate Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

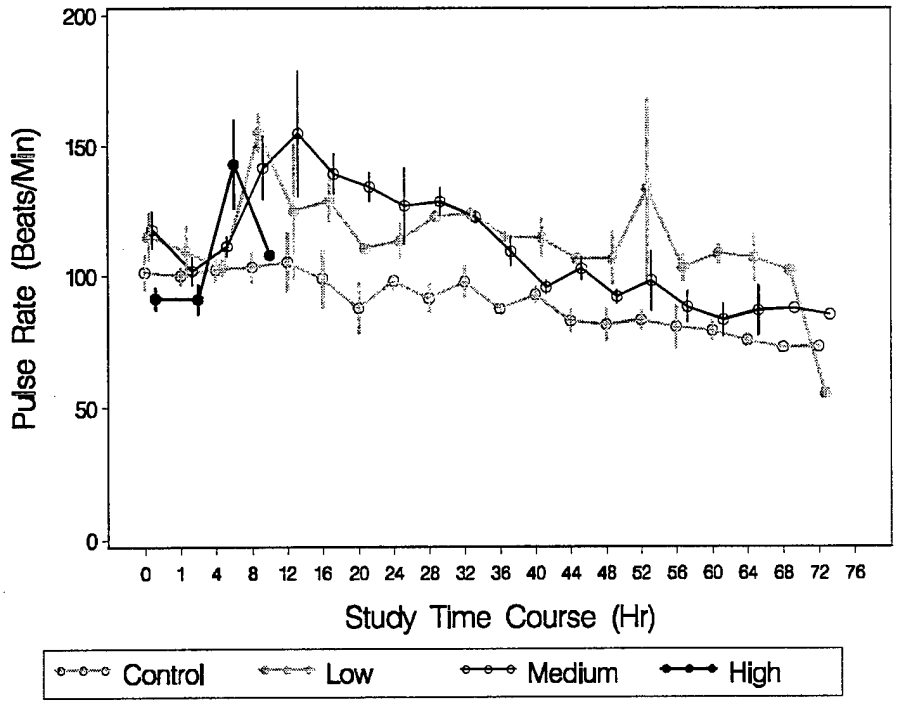

Figure 4e. **Pulse Rate Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups**

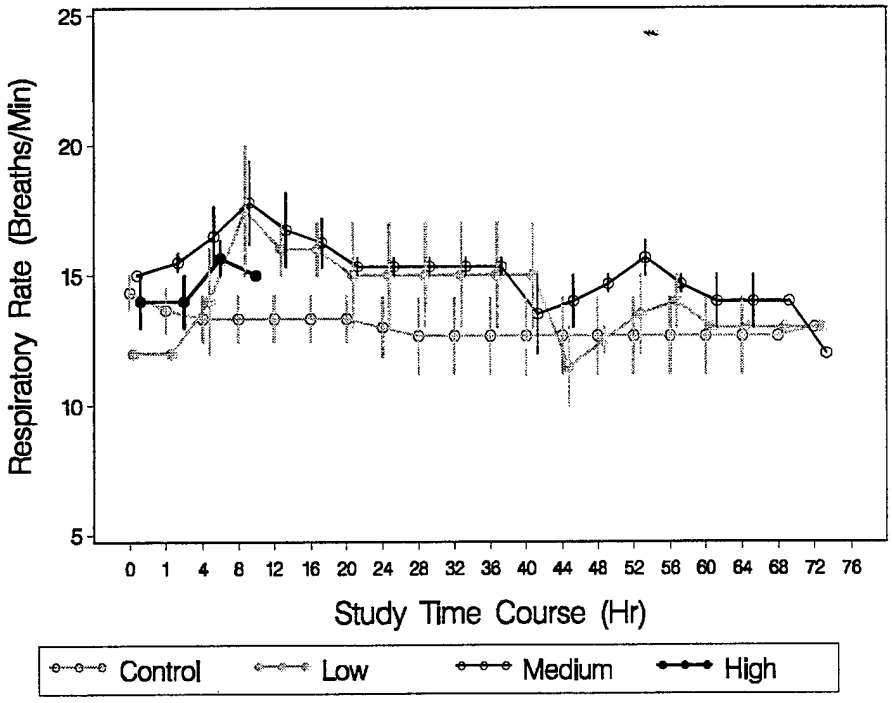

Figure 4f. **Respiratory Rate Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups**

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

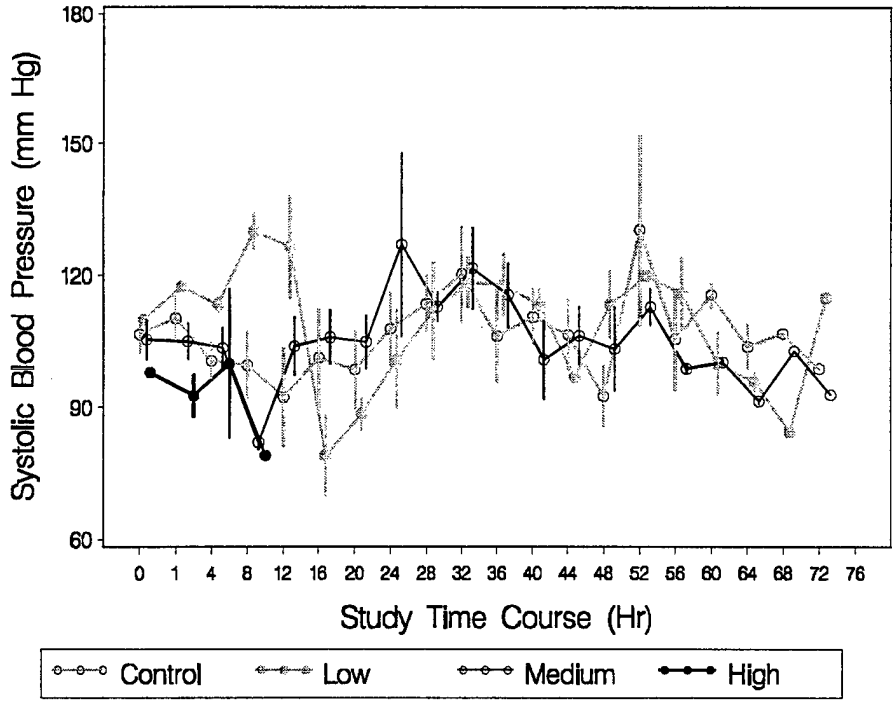

Figure 4g. Systolic Blood Pressure Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

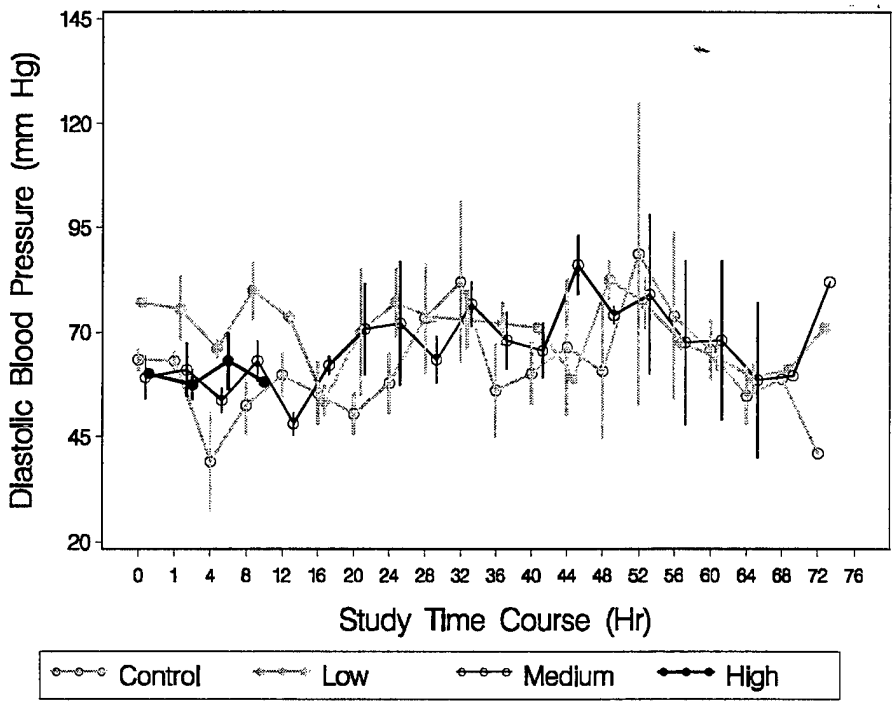

Figure 4h. Diastolic Blood Pressure Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

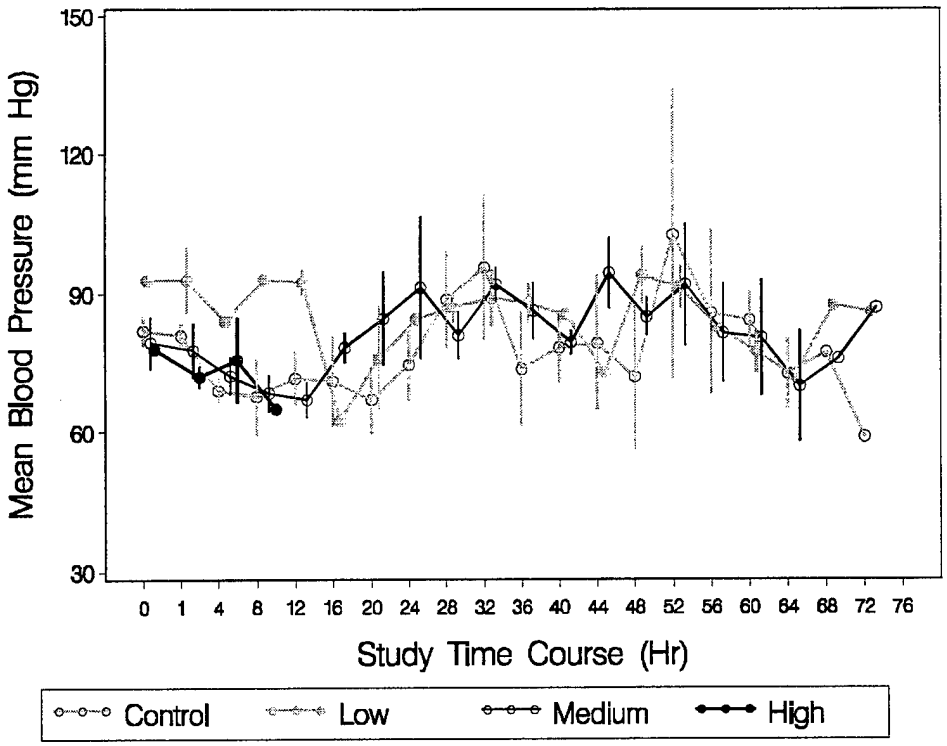

Figure 4i. Mean Blood Pressure Values in Anesthetized, Ventilated Swine in Air Control and CG-Exposed Groups

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

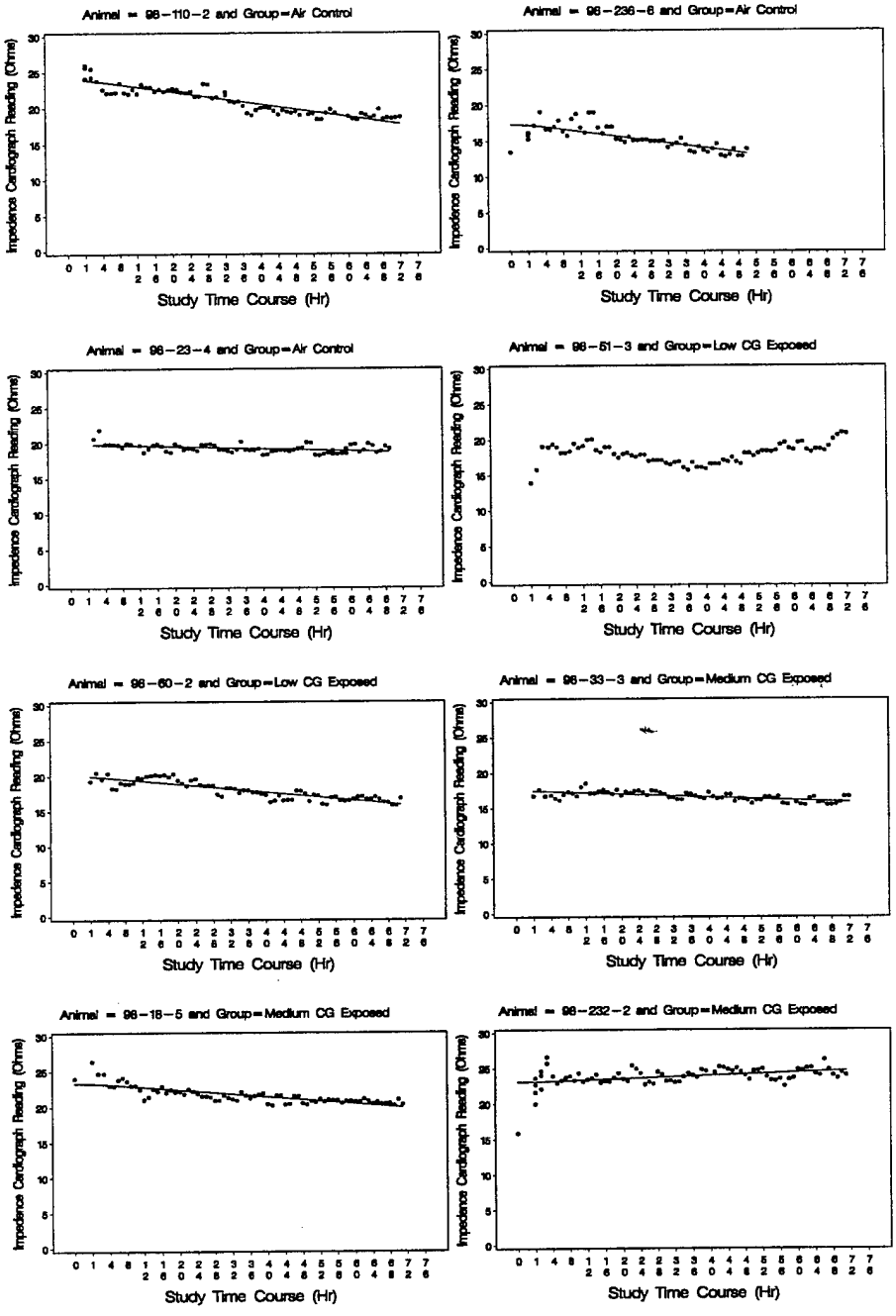

Figure 5a. Impedance Cardiograph Versus Study Time Course with Regression Line by Animal in Anesthetized, Ventilated Swine in Air Control and Low and Medium (Lived) CG-Exposed Groups

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

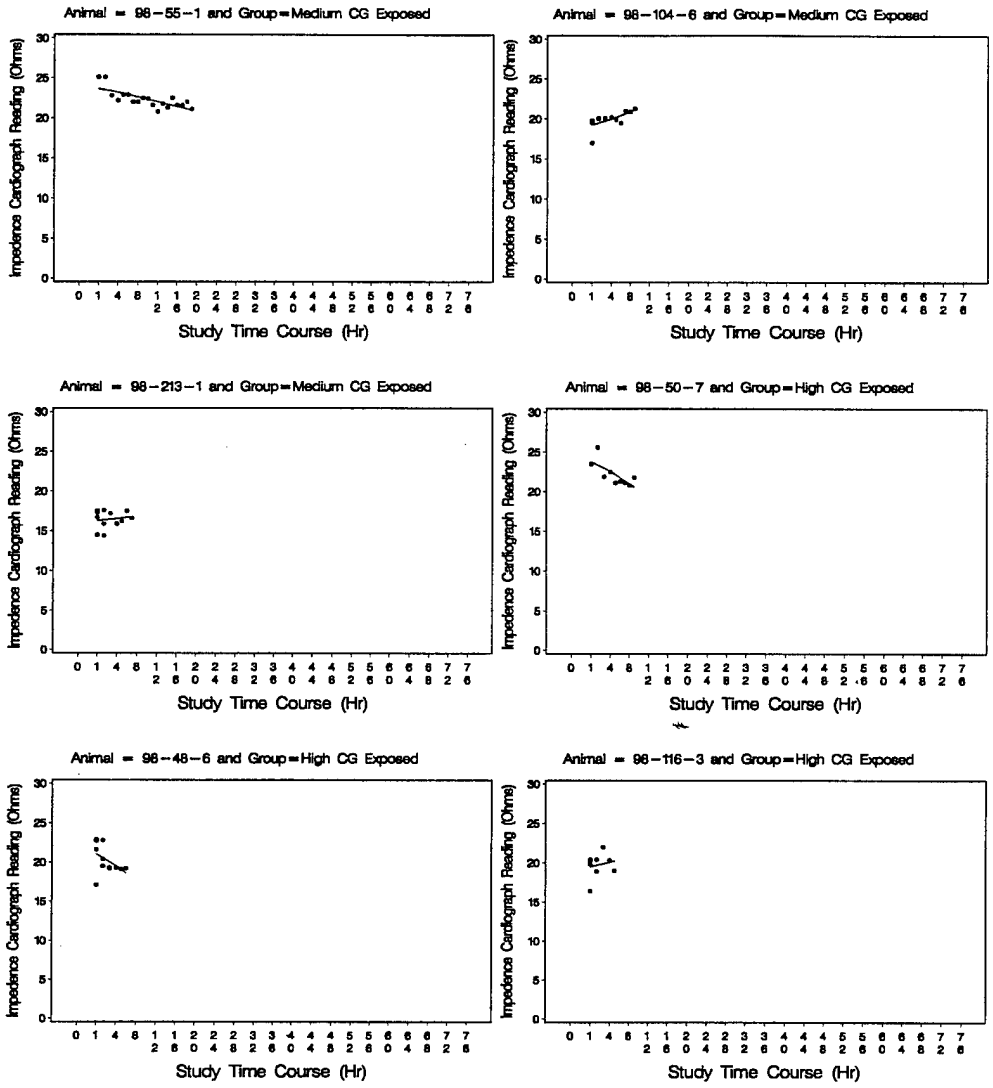

Figure 5b. Impedance Cardiograph Versus Study Time Course with Regression Line by Animal in Medium (Died) and High CG-Exposed Groups

Control: n=3; air exposure
Low: n=2; 2450-3300 mg/m^3 · min CG exposure
Medium: n=6; 3700-4500 mg/m^3 · min CG exposure
High: n=3; 4900-5600 mg/m^3 · min CG exposure

ATTACHMENT E

EXPOSURE TABLES
PHASE I AND PHASE II DATA

TABLE E. 1. TABLE OF PHASE I ANESTHETIC ADMINISTRATION AND SURVIVAL TIMES

Test No.	Phase	Date	Type	Pig ID	Pig Weight (Kg)	Observations
1	I	25-Feb-98	Anesthesia	98-47-7	21.1	Dead Mucal plug resulting in respiratory distress and cardiovascular collapse. Anesthetized 22 hr 32 min. Pentobarbital - 17 hr 42 min.
2	I	23-Mar-98	Anesthesia	98-105-3	16.8	Dead Mucal plug resulting in respiratory distress and cardiovascular collapse. Anesthetized 37 hr 2 min. Pentobarbital - 34 hr 52 min.
3	I	7-Apr-98	Anesthesia	98-345-5	19.1	Survived. Anesthetized 73 hr 15 min. Pentobarbital - 71 hr 15 min.
4	I	14-Apr-98	Anesthesia	98-37-3	19.1	DEAD from ruptured bladder. Anesthetized 34 hr. Pentobarbital - 32 hr.
5	I	27-Apr-98	Anesthesia	98-24-4	18.2	Survived. Anesthetized 74 hr 58 min. Pentobarbital - 72 hr 16 min.
6	I	4-May-98	Anesthesia	98-23-4	20.0	Survived. Anesthetized 73 hr 59 min. Pentobarbital - 73 hr 9 min.
7	I	11-May-98	Anesthesia	98-327-6	18.6	Survived. Anesthetized 72 hr 20 min. Pentobarbital - 70 hr 57 min.
8	I	9-Jun-98	Oleic Acid	98-34-6	20.5	DEAD 2 min after last oleic infusion (admin. 3 mL over 1.5 hr) due to pulmonary edema.

TABLE E. 2. AIR AND PHOSGENE EXPOSURES AND SURVIVAL TIMES

Test No.	Phase	Dates	Type	Phosgene Conc. (mg/m^3)		During (min)	Animal Wt (kg)	Exposure ($mg \cdot min/m^3$)	Pig ID	Observations
				Target	Actual					
1	I	22-Jun-98	Phosgene	1,000	937	10	17.3	9,370	98-45-3	DEAD when removed from hood. Incorrect respirator setting fatally injured lungs.
2	I	29-Jun-98	Phosgene	250	NA	NA	18.2	NA	98-44-3	NO TEST. Animal died prior to exposure. Thought to be due to new anesthesia method.
3	I	7-Jul-98	Phosgene	250	245	10	20.9	2,450	98-51-3	Lived over complete 72 hours observation period.
4	I	13-Jul-98	Phosgene	500	493	10	16.4	4,930	98-50-7	DEAD 9 hours post exposure due to pulmonary edema.
5	I	21-Jul-98	Phosgene	375	371	10	20.0	3,710	98-55-1	DEAD approximately 20 hours 35 min post exposure due to pulmonary edema.
6	I	3-Aug-98	Phosgene	325	329	10	18.2	3,290	98-60-2	Lived over complete 72 hours observation period.
7	I	17-Aug-98	Phosgene	375	377	10	20.0	3,770	98-33-3	Lived over complete 72 hours observation period.
8	I	31-Aug-98	Phosgene	550	557	10	19.1	5,570	98-48-6	DEAD 6 hours 19 min post exposure due to pulmonary edema.
9	I	14-Sept-98	Phosgene	425	425	10	19.5	4,250	98-104-6	DEAD 8 hours 44 min post exposure due to pulmonary edema.

TABLE E. 2. AIR AND PHOSGENE EXPOSURES AND SURVIVAL TIMES (Continued)

Test No.	Phase	Dates	Type	Phosgene Conc. (mg/m^3)		During (min)	Animal Wt (kg)	Exposure ($mg \cdot min/m^3$)	Pig ID	Observations
				Target	Actual					
10	I	12-Oct-98	Phosgene	425	NA	NA	17.3	NA	98-114-1	Pig died prior to exposure due to massive blood loss from the arterial catheter incision. The catheter came out and the attempts to replace it and contain the bleeding were unsuccessful.
11	I	26-Oct-98	Phosgene	425	420	10	20.5	4,200	98-18-5	Lived over complete 72 hours observation period.
12	I	2-Nov-98	Phosgene	500	491	10	18.6	4,910	98-116-3	DEAD 6 hours 27 min post exposure due to pulmonary edema.
13	I	9-Nov-98	IBU	500	497	10	20.0	4,970	98-116-1	DEAD 4 hours 27 min post exposure due to pulmonary edema.
14	II	23-Nov-98	Phosgene	450	449	10	19.1	4,490	98-213-1	DEAD 8 hours 14 min post exposure due to pulmonary edema.

Table E. 3. PHASE II List of Anesthetized, Ventilated Swine Exposed to Air or Phosgene per Treatment Group. Includes replaced animals with reason for replacement

AIR			PHOSGENE		
1. 98-110-2	9/21/98	72 hr	98-213-1	11/23/98	8 hr 14 min
2. 98-236-6	1/4/99	72 hr	98-232-2	12/28/98	72 hr
3. 99-251-6	2/8/99	72 hr	99-255-3	2/8/99	12 hr 54 min
4. 99-21-1	4/5/99	72 hr	99-21-2	4/5/99	13 hr 30 min
5. 99-288-4	5/10/99	72 hr	99-92-6	5/10/99	20 hr 4 min
6. 99-287-1	6/1/99	72 hr	99-287-2	6/1/99	22 hr 40 min

AIR + NAC			PHOSGENE + NAC		
1. 98-241-1	1/12/99	72 hr	98-241-6	1/12/99	12 hr 22 min
2. 99-253-1	2/1/99	72 hr	98-249-1	1/18/99	72 hr
3.			99-249-5	1/25/99	4 hr 33 min
4. Air+NAC AND Phos+NAC Stopped – Survival is minimally effective.					
5.					
6.					

AIR + IBU-45 & 22.5 mg/kg every 2 hr			PHOSGENE + IBU		
1. 99-272-2	3/29/99	72 hr	99-272-3	3/29/99	72 hr
2. 99-293-2	5/17/99	72 hr	99-272-4	4/12/99	7 hr 48 min
3. 99-146-3	6/28/99	72 hr	99-111-4	5/3/99	72 hr
4. 99-136-1	7/6/99	27 hr 4 min	99-294-3	5/17/99	27 hr 43 min
5. 99-150-3	7/12/99	9 hr 38 min	99-136-6	7/6/99	6 hr 56 min
6.			99-153-3	7/12/99	11 hr 52 min

PHOSGENE + 10-15 cm PEEP + O_2

1. 98-116-2	11/16/98	14 hr 37 min
2. 98-247-1	1/18/99	72 hr
3. 99-256-4	2/15/99	4 hr 5 min
4. 99-259-2	2/22/99	6 hr 2 min
5. Phos+PEEP+AIR stopped		
6.		

DATA EXCLUDED AND NOT ANALYZED

This list contains the animals that were excluded from the data analyses and the reason why. To summarize the reason for exclusion is as follows: Animals that were administered various dosing regimens and concentrations of IBU to determine the study dosage, over-inflation of the lungs, pre-existing disease condition (such as urinary bladder thickening or ulceration/infection, gaseous distension of the bowel with or without hyperkalemia, pneumonia or upper respiratory tract infection/inflammation at or before the time of exposure, and missed treatments or too many data points due to mechanical failure.

1. 98-220-3	11/30/98	72 hr - Air+IBU 100 then 50 mg/kg every 4 hr Tx
2. 98-221-6	12/7/98	72 hr - Phos+IBU 100 then 50 mg/kg every 4 hr Tx
3. 98-222-6	12/14/98	3 hr 58 min - PEEP+ O_2 overinflated lungs - REPEAT
4. 98-246-1	1/25/99	7 hr 50 min - Phos+IBU 100 then 50 mg/kg every 4 hr Tx

TABLE E. 3.
(Continued)

5. 99-253-3 2/1/99 7 hr 27 min - Phos+IBU 100 then 50 mg/kg every 4 hr Tx
6. 99-256-1 2/15/99 72 hr - Air+IBU 100 then 50 mg/kg every 4 hr Tx
7. 99-259-1 2/22/99 6 hr 34 min - Phos+IBU 100 then 50 mg/kg every 4 hr Tx
8. 99-260-2 3/1/99 6 hr 33 min - Air+IBU 100 mg/kg continuous Tx
9. 99-262-3 3/1/99 4 hr 27 min - Phos+IBU 100 mg/kg continuous Tx
10. 99-263-2 3/8/99 16 hr 1 min - Air+IBU 65 mg/kg continuous Tx
11. 99-263-1 3/8/99 4 hr 14 min - Phos+IBU 65 mg/kg continuous Tx
12. 99-272-5 4/12/99 euthanatized - Air+IBU 45 then 22.5 mg/kg every 2 hr Tx – TX missed, REPEAT
13. 99-111-3 5/3/99 13 hr 34 min - Air+IBU 45 then 22.5 mg/kg every 2 hr Tx – Urinary bladder thickened and infected, REPEAT
14. 99-298-2 5/24/99 euthanatized - Air+IBU 45 then 22.5 mg/kg every 2 hr Tx – Pneumonia, REPEAT
15. 99-298-1 5/24/99 5 hr 36 min - Phos+IBU 45 then 22.5 mg/kg every 2 hr Tx – Gaseous distension of bowel, Hyperkalemia - REPEAT
16. 99—31-5 6-7-99 13 hr 54 min - Air+IBU 45 then 22.5 mg/kg every 2 hr Tx – Ulcerated urinary bladder – REPEAT
17. 99-31-3 6-7-99 6 hr 31 min - 45 then 22.5 mg/kg every 2 hr Tx – Ulcerated urinary bladder – REPEAT
18. 99-139-4 6-14-99 euthanatized - Inflammation of the lungs during quarantine – REPEAT
19. 99-135-1 6-14-99 euthanatized - Inflammation of the lungs during quarantine – REPEAT
20. 99-41-4 6-21-99 33 hr 33 min - Air+IBU 45 then 22.5 mg/kg every 2 hr Tx – Gaseous distension of bowel – REPEAT
21. 99-140-1 6-21-99 5 hr 26 min - Phos+IBU 45 then 22.5 mg/kg every 2 hr Tx – Urinary bladder intact (no puncture) – REPEAT
22. 99-147-2 6-28-99 5 hr 20 min - Phos+IBU 45 then 22.5 mg/kg every 2 hr Tx – Respiratory inflammation – REPEAT

TABLE E. 4. TABLE OF PHASE II EXPOSURE CONCENTRATIONS TO AIR OR PHOSGENE AND SURVIVAL TIME AFTER TREATMENT FOR EACH ANIMAL

Test #	Date	Type	Phosgene Conc. (mg/m^3)		Exposure Times			Exposure ($mg \cdot min/m^3$)	Pig ID	Observations
			Target	Actual	Start (h:m)	Stop (h:m)	Dur. (min)			
1	21-Sept-98	Air	0	0	11:32	11:42	10	0	98-110-2	Lived over complete 72 hr observation period.
2	16-Nov-98	PEEP/O_2	450	453	11:19	11:29	10	4,530	98-116-2	Survived 14 hr 37 min post exposure - pulmonary edema.
3	23-Nov-98	Phosgene	450	449	11:24	11:34	10	4,490	98-213-1	Survived 8 hr 14 min post exposure - pulmonary edema.
4	30-Nov-98	Air-IBU	0	0	10:55	11:05	10	0	98-220-3	Lived over complete 72 hr observation period.
5	7-Dec-98	IBU	450	449	11:07	11:17	10	4,490	98-221-6	Lived over complete 72 hr observation period.
6	14-Dec-98	PEEP/O_2	450	446	11:51	12:01	10	4,460	98-222-6	Survived 3 hr 58 min post exposure - pulmonary edema and over inflation of the lungs – **REPEAT**.
7	28-Dec-98	Phosgene	450	452	11:14	11:24	10	4,520	98-232-2	Lived over complete 72 hr observation period.
8	4-Jan-99	Air	0	0	11:15	11:25	10	0	98-236-6	Lived over complete 72 hr observation period.
9	12-Jan-99	Air/NAC	0	0	11:54	12:04	10	0	98-241-1	Lived over complete 72 hr observation period.
10	12-Jan-99	NAC	450	449	14:47	14:57	10	4,490	98-241-6	Survived 12 hr 22 min post exposure - pulmonary edema.
11	18-Jan-99	PEEP/O_2	450	453	10:45	10:55	10	4,530	98-247-1	Repeat of animal 98-222-6. Lived over complete 72 hr observation period.
12	18-Jan-99	NAC	450	453	13:00	13:10	10	4,530	98-249-1	Lived over complete 72 hr observation period.
13	25-Jan-99	IBU	450	450	11:54	12:04	10	4,500	99-246-1	Survived 7 hr 50 min post exposure - pulmonary edema.
14	25-Jan-99	NAC	450	450	14:22	14:32	10	4,500	99-249-5	Survived 4 hr 33 min post exposure - pulmonary edema.
15	1-Feb-99	Air/NAC	0	0	11:30	11:40	10	0	99-253-1	Lived over complete 72 hr observation period.
16	1-Feb-99	IBU	450	456	14:42	14:52	10	4,560	99-253-3	Survived 7 hr 27 min post-exposure – pulmonary edema.
17	8-Feb-99	Air	0	0	11:35	11:45	10	0	99-251-6	Lived over complete 72 hr observation period.
18	8-Feb-99	Phosgene	450	450	13:33	13:43	10	4,500	99-255-3	Survived 12 hr 54 min post exposure – pulmonary edema.
19	15-Feb-99	Air/IBU	0	0	11:49	11:59	10	0	99-256-1	Lived over complete 72 hr observation period.
20	15-Feb-99	PEEP/O_2	450	447	14:36	14:46	10	4,470	99-256-4	Survived 4 hr 5 min post exposure – pulmonary edema.
21	22-Feb-99	IBU	450	450	11:07	11:17	10	4,500	99-259-1	Survived 6 hr 34 min post exposure – pulmonary edema.
22	22-Feb-99	PEEP/O_2	450	456	13:06	13:16	10	4,560	99-259-2	Survived 6 hr 2 min post exposure – pulmonary edema.
23	1-Mar-99	Air/IBU	0	0	10:57	11:07	10	0	99-260-2	Survived 6 hr 33 min post exposure – pulmonary edema.
24	1-Mar-99	IBU	450	449	12:46	12:56	10	4,490	99-262-3	Survived 4 hr 27 min post exposure – pulmonary edema.

TABLE E. 4. TABLE OF PHASE II EXPOSURE CONCENTRATIONS TO AIR OR PHOSGENE AND SURVIVAL TIME AFTER TREATMENT FOR EACH ANIMAL (Continued)

Test #	Date	Type	Phosgene Conc. (mg/m^3)		Exposure Times			Exposure ($mg \cdot min/m^3$)	Pig ID	Observations
			Target	Actual	Start (h:m)	Stop (h:m)	Dur. (min)			
25	8-Mar-99	Air/IBU	0	0	10:40	10:50	10	0	99-263-2	Survived 16 hr 1 min post exposure – pulmonary edema.
26	8-Mar-99	IBU	450	458	13:19	13:29	10	4,580	99-263-1	Survived 4 hr 14 min post exposure – pulmonary edema.
27	29-Mar-99	Air/IBU	0	0	10:55	11:05	10	0	99-272-2	Lived over complete 72 hr observation period.
28	29-Mar-99	IBU	450	430-500 (450)	13:01	13:11	10	4,300-5,000 (4,500)	99-272-3	Lived over complete 72 hr observation period.
29	5-Apr-99	Air	0	0	10:38	10:48	10	0	99-21-1	Lived over complete 72 hr observation period.
30	5-Apr-99	Phosgene	450	449	12:35	12:45	10	4,490	99-21-2	Survived 13 hr 30 min post exposure – pulmonary edema.
31	12-Apr-99	Air/IBU	0	0	10:54	11:04	10	0	99-272-5	Euthanitized since treatments and blood samples were missed. **REPEAT**
32	12-Apr-99	IBU	450	451	12:50	13:00	10	4,510	99-272-4	Survived 7 hr 48 min post exposure – pulmonary edema.
33	3-May-99	Air/IBU	0	0	11:23	11:33	10	0	99-111-3	Survived 13 hr 34 min post exposure – urinary bladder infection. **REPEAT**
34	3-May-99	IBU	450	449	13:13	13:23	10	4,490	99-111-4	Lived over complete 72 hr observation period
35	10-May-99	Air	0	0	10:36	10:46	10	0	99-288-4	Lived over complete 72 hr observation period
36	10-May-99	Phosgene	450	452	13:59	14:09	10	4,520	99-92-6	Survived 20 hr 4 min post exposure – pulmonary edema.
37	17-May-99	Air/IBU	0	0	10:46	10:56	10	0	99-293-2	Lived over complete 72 hr observation period
38	17-May-99	IBU	450	451	13:19	13:29	10	4,510	99-294-3	Survived 27 hr 43 min post exposure – pulmonary edema.
39	24-May-99	Air/IBU	0	0	10:39	10:49	10	0	99-298-2	Euthanitized after approximately 45 hr 36 min as a result of pneumonia and upper respiratory infection. **REPEAT**
40	24-May-99	IBU	450	451	1251	1301	10	4,510	99-298-1	Survived 5 hr 36 min – missed treatment, gaseous distension of bowel, hyperkalemia – **REPEAT**
41	1-Jun-99	Air	0	0	10:24	10:34	10	0	99-287-1	Survived 72 hr observation period.
42	1-Jun-99	Phosgene	450	451	12:39	12:49	10	4,510	99-287-2	Survived 22 hr 40 min.
43	7-Jun-99	Air/IBU	0	0	10:30	10:40	10	0	99-31-5	Survived 13 hr 54 min – ulcerated urinary bladder. **REPEAT**
44	7-Jun-99	IBU	450	448	12:25	12:35	10	4,480	99-31-3	Survived 6 hr 31 min – ulcerated urinary bladder. **REPEAT**
45	14-Jun-99	NA	NA	NA	NA	NA	10	NA	99-139-4	Repeat animal 99-272-5. Euthanitized – respiratory. **REPEAT**

TABLE E. 4. TABLE OF PHASE II EXPOSURE CONCENTRATIONS TO AIR OR PHOSGENE AND SURVIVAL TIME AFTER TREATMENT FOR EACH ANIMAL (Continued)

Test #	Date	Type	Phosgene Conc. (mg/m^3)		Exposure Times			Exposure ($mg \cdot min/m^3$)	Pig ID	Observations
			Target	Actual	Start (h:m)	Stop (h:m)	Dur. (min)			
46	14-Jun-99	NA	NA	NA	NA	NA	10	NA	99-135-1	Repeat animal 99-298-1. Euthanitized – respiratory. **REPEAT**
47	21-Jun-99	Air/IBU	0	0	1010	1020	10	0	99-41-4	Repeat of animal 99-272-5. Survived 33 hr 33 min – gaseous distension of bowel. **REPEAT**
48	21-Jun-99	IBU	450	450	1259	1309	10	4,500	99-140-1	Repeat of animal 99-298-1. Survived 5 hr 26 min – urinary bladder intact, missed catheter placement. **REPEAT**
49	28-Jun-99	Air/IBU	0	0	1026	1036	10	0	99-146-3	Repeat animal 99-272-5. Lived over complete 72 hr observation period.
50	28-Jun-99	IBU	450	450	1239	1249	10	4,500	99-147-2	Repeat animal 99-298-1. Survived 5 hr 20 min – respiratory Inflammation. **REPEAT**
51	6-Jul-99	Air/IBU	0	0	1016	1026	10	0	99-136-1	Repeat animal 99-111-3. Survived 27 hr 4 min – hyperkalemia.
52	6-Jul-99	IBU	450	447	1322	1332	10	4,470	99-136-6	Repeat animal 99-298-1. Survived 6 hr 56 min – pulmonary edema.
53	12-Jul-99	Air/IBU	0	0	1026	1036	10	0	99-150-3	Repeat animal 99-298-2. Survived 9 hr 38 min – hyperkalemia.
54	12-Jul-99	IBU	450	451	1305	1315	10	4,510	99-153-3	Repeat animal 99-31-3. Survived 11 hr 52 min – pulmonary edema

Table of Wet/Dry Weights and their Ratio For Each Animal In Each Treatment Group Used in Statistical Analysis in Phase II
Included are only data for animals used in statistical analysis.

Treatment Key
Ibuprofen = IBU
N-Acetylcysteine = NAC
Positive end expiratory pressure and 45% Oxygen = PEEP

Animal #	Date exposed	Exposure Phos/Air	Treatment	Live weight kg	Dead weight kg	Lung ID	Wet Wt (gm)	Dry Wt (gm)	(Wet-Dry)/Dry Ratio (gm)			
99-272-2	03/29/1999	air	IBU	15.9	20.5	RML	20.9	3.8	4.5			
99-272-2	03/29/1999	air	IBU			LCL	8.1	1.4	4.8		AVG	STD
99-272-2	03/29/1999	air	IBU			LCdL	6.2	1.1	4.6	Wet Wt	13.91429	8.69395
99-272-2	03/29/1999	air	IBU			RMR	25.6	4.5	4.7	Dry Wt	2.457143	1.537159
99-272-2	03/29/1999	air	IBU			LCR	9.7	1.6	5.1	(W-D)/D R	4.6	0.290823
99-272-2	03/29/1999	air	IBU			LCdR	22.3	3.9	4.7			
99-272-2	03/29/1999	air	IBU			RAc	4.6	0.9	4.1			
99-293-2	05/17/1999	air	IBU	17.3	18.2	RML	13.2	2.1	5.3			
99-293-2	05/17/1999	air	IBU			LCL	7	1.1	5.4		AVG	STD
99-293-2	05/17/1999	air	IBU			LCdL	22.9	3.6	5.4	Wet Wt	19.37143	13.09895
99-293-2	05/17/1999	air	IBU			RMR	35	5.6	5.3	Dry Wt	3.085714	2.119299
99-293-2	05/17/1999	air	IBU			LCR	13.2	2.1	5.3	W/D R	5.3	0.116823
99-293-2	05/17/1999	air	IBU			LCdR	38.4	6.2	5.2			
99-293-2	05/17/1999	air	IBU			RAc	5.9	0.9	5.6			
99-146-3	06/28/1999	air	IBU	18.2	19.5	RCL	22.6	3.1	6.3			
99-146-3	06/28/1999	air	IBU			RCdL	29.8	4.3	5.9		AVG	STD
99-146-3	06/28/1999	air	IBU			LML	33.6	4.8	6.0	Wet Wt	31.45714	12.98857
99-146-3	06/28/1999	air	IBU			RCR	35.7	5	6.1	Dry Wt	4.5	1.967232
99-146-3	06/28/1999	air	IBU			RCdR	42.3	6.1	5.9	W/D R	6.1	0.327359
99-146-3	06/28/1999	air	IBU			LMR	47.7	7.1	5.7			
99-146-3	06/28/1999	air	IBU			RAc	8.5	1.1	6.7			
99-136-1	07/06/1999	air	IBU	16.4	17.5	RCL	18.6	3	5.2			
99-136-1	07/06/1999	air	IBU			RCdL	23.9	4.3	4.6		AVG	STD
99-136-1	07/06/1999	air	IBU			LML	22.2	4.2	4.3	Wet Wt	14.97143	6.832695
99-136-1	07/06/1999	air	IBU			RCR	10.7	1.9	4.6	Dry Wt	2.671429	1.253946
99-136-1	07/06/1999	air	IBU			RCdR	9.3	1.7	4.5	W/D R	4.6	0.294286
99-136-1	07/06/1999	air	IBU			LMR	14.3	2.6	4.5			
99-136-1	07/06/1999	air	IBU			LAc	5.8	1	4.8			
99-150-3	07/12/1999	air	IBU	19.5	20.7	RML	13.1	2	5.6			
99-150-3	07/12/1999	air	IBU			LCL	16.5	2.7	5.1		AVG	STD
99-150-3	07/12/1999	air	IBU			LCdL	31.6	4.1	6.7	Wet Wt	16.28571	8.91
99-150-3	07/12/1999	air	IBU			RMR	24	4.1	4.9	Dry Wt	2.557143	1.198412
99-150-3	07/12/1999	air	IBU			LCR	11.6	2	4.8	W/D R	5.2	0.719597
99-150-3	07/12/1999	air	IBU			LCdR	12.6	2.2	4.7			
99-150-3	07/12/1999	air	IBU			LAc	4.6	0.8	4.8			
98-110-2	09/21/1998	air	NA	19.5	NA	RML	21.9	3.5	5.3			
98-110-2	09/21/1998	air	NA			LCL	20.8	3.2	5.5		AVG	STD
98-110-2	09/21/1998	air	NA			LCdL	15.7	2.4	5.5	Wet Wt	16.54286	7.095505
98-110-2	09/21/1998	air	NA			RCR	8.7	1.4	5.2	Dry Wt	2.6	1.140175
98-110-2	09/21/1998	air	NA			RCdR	25.7	4.1	5.3	W/D R	5.4	0.210075
98-110-2	09/21/1998	air	NA			LMR	16.9	2.7	5.3			
98-110-2	09/21/1998	air	NA			LAc	6.1	0.9	5.8			
98-236-6	01/04/1999	air	NA	19.5	20	RCL	23.5	3.3	6.1			
98-236-6	01/04/1999	air	NA			RCdL	24.6	4.1	5.0		AVG	STD
98-236-6	01/04/1999	air	NA			LML	20.5	3.1	5.6	Wet Wt	25.17143	9.554181
98-236-6	01/04/1999	air	NA			RMR	36.3	5.4	5.7	Dry Wt	3.771429	1.392497
98-236-6	01/04/1999	air	NA			LCR	30.1	4.5	5.7	W/D R	5.6	0.368653
98-236-6	01/04/1999	air	NA			LCdR	33.5	4.8	6.0			
98-236-6	01/04/1999	air	NA			RAc	7.7	1.2	5.4			
99-251-6	02/08/1999	air	NA	21.4	21.4	RML	34	4.7	6.2			
99-251-6	02/08/1999	air	NA			LCL	13.8	1.9	6.3		AVG	STD
99-251-6	02/08/1999	air	NA			LCdL	22.3	3	6.4	Wet Wt	25.85714	11.97857
99-251-6	02/08/1999	air	NA			RCR	19.6	2.5	6.8	Dry Wt	3.5	1.640122
99-251-6	02/08/1999	air	NA			RCdR	31.9	4.2	6.6	W/D R	6.4	0.260938
99-251-6	02/08/1999	air	NA			LMR	46	6.3	6.3			
99-251-6	02/08/1999	air	NA			LAc	13.4	1.9	6.1			
99-21-1	04/05/1999	air	NA	17.7	18.2	RCL	20.8	3	5.9			
99-21-1	04/05/1999	air	NA			RCdL	12.9	2	5.5		AVG	STD
99-21-1	04/05/1999	air	NA			LML	36.5	5.4	5.8	Wet Wt	21.67143	11.92095
99-21-1	04/05/1999	air	NA			RMR	33.7	5	5.7	Dry Wt	3.228571	1.767969
99-21-1	04/05/1999	air	NA			LCR	14.9	2.2	5.8	W/D R	5.7	0.155895
99-21-1	04/05/1999	air	NA			LCdR	28.9	4.4	5.6			
99-21-1	04/05/1999	air	NA			RAc	4	0.6	5.7			

TABLE E. 5.

Animal #	Date exposed	Exposure Phos/Air	Treatment	weight kg	weight kg	Lung ID	Wet Wt (gm)	Dry Wt (gm)	(Wet-Dry)/Dry Ratio (gm)
99-288-4	05/10/1999	air	NA	15.9	15.9	RML	11.1	1.7	5.5
99-288-4	05/10/1999	air	NA			LCL	3.9	0.6	5.5
99-288-4	05/10/1999	air	NA			LCdL	21.9	3.5	5.3
99-288-4	05/10/1999	air	NA			RCR	5	0.8	5.3
99-288-4	05/10/1999	air	NA			RCdR	18.1	2.8	5.5
99-288-4	05/10/1999	air	NA			LMR	23.1	3.6	5.4
99-288-4	05/10/1999	air	NA			LAc	7.4	1.2	5.2
99-287-1	06/01/1999	air	NA	21	21.4	RCL	13.9	1.9	6.3
99-287-1	06/01/1999	air	NA			RCdL	26.6	4.2	5.3
99-287-1	06/01/1999	air	NA			LML	31.5	5	5.3
99-287-1	06/01/1999	air	NA			RMR	45.3	6.7	5.8
99-287-1	06/01/1999	air	NA			LCR	20.3	2.3	7.8
99-287-1	06/01/1999	air	NA			LCdR	32.8	4.9	5.7
99-287-1	06/01/1999	air	NA			RAc	9	1.3	5.9
98-241-1	01/12/1999	air	NAC	21	20.4	RML	30.7	5.1	5.0
98-241-1	01/12/1999	air	NAC			LCL	16	2.5	5.4
98-241-1	01/12/1999	air	NAC			LCdL	15.9	2.6	5.1
98-241-1	01/12/1999	air	NAC			RCR	17.7	2.8	5.3
98-241-1	01/12/1999	air	NAC			RCdR	18.3	3	5.1
98-241-1	01/12/1999	air	NAC			LMR	41.7	6.8	5.1
98-241-1	01/12/1999	air	NAC			LAc	7.9	1.2	5.6
99-253-1	02/01/1999	air	NAC	20.5	20	RCL	11.5	1.5	6.7
99-253-1	02/01/1999	air	NAC			RCdL	38.4	5.2	6.4
99-253-1	02/01/1999	air	NAC			LML	43	6.3	5.8
99-253-1	02/01/1999	air	NAC			RMR	45.8	6	6.6
99-253-1	02/01/1999	air	NAC			LCR	19.4	2.5	6.8
99-253-1	02/01/1999	air	NAC			LCdR	47.1	7.1	5.6
99-253-1	02/01/1999	air	NAC			RAc	10.7	1.4	6.6
99-272-3	03/29/1999	phosgene	IBU	17.3	18.2	RML	57.6	7.5	6.7
99-272-3	03/29/1999	phosgene	IBU			LCL	14.5	1.9	6.6
99-272-3	03/29/1999	phosgene	IBU			LCdL	20.5	2.5	7.2
99-272-3	03/29/1999	phosgene	IBU			RMR	65.3	8.5	6.7
99-272-3	03/29/1999	phosgene	IBU			LCR	17.2	2.3	6.5
99-272-3	03/29/1999	phosgene	IBU			LCdR	53	6.7	6.9
99-272-3	03/29/1999	phosgene	IBU			RAc	11.9	1.5	6.9
99-272-4	04/12/1999	phosgene	IBU	19.5	20.5	RML	25.1	3	7.4
99-272-4	04/12/1999	phosgene	IBU			LCL	20.4	2.7	6.6
99-272-4	04/12/1999	phosgene	IBU			LCdL	20.6	2.6	6.9
99-272-4	04/12/1999	phosgene	IBU			RCR	11.5	1.6	6.2
99-272-4	04/12/1999	phosgene	IBU			RCdR	29.4	4.2	6.0
99-272-4	04/12/1999	phosgene	IBU			LMR	25.6	3.5	6.3
99-272-4	04/12/1999	phosgene	IBU			LAc	9.1	0.9	9.1
99-111-4	05/03/1999	phosgene	IBU	20.5	19.5	RCL	18.3	2.9	5.3
99-111-4	05/03/1999	phosgene	IBU			RCdL	23.5	3.9	5.0
99-111-4	05/03/1999	phosgene	IBU			LML	24.4	4	5.1
99-111-4	05/03/1999	phosgene	IBU			RCR	24.5	3.9	5.3
99-111-4	05/03/1999	phosgene	IBU			RCdR	4.9	0.8	5.1
99-111-4	05/03/1999	phosgene	IBU			LMR	33.1	5.7	4.8
99-111-4	05/03/1999	phosgene	IBU			LAc	5.3	0.9	4.9
99-294-3	05/17/1999	phosgene	IBU	19.5	20.7	RML	24.8	3.1	7.0
99-294-3	05/17/1999	phosgene	IBU			LCL	12.4	1.7	6.3
99-294-3	05/17/1999	phosgene	IBU			LCdL	27.2	3.6	6.6
99-294-3	05/17/1999	phosgene	IBU			RMR	44.4	5.7	6.8
99-294-3	05/17/1999	phosgene	IBU			LCR	36.3	4.2	7.6
99-294-3	05/17/1999	phosgene	IBU			LCdR	33.3	3.9	7.5
99-294-3	05/17/1999	phosgene	IBU			RAc	8.3	1.1	6.5
99-136-6	07/06/1999	phosgene	IBU	21.6	22.7	RCL	26.8	3.2	7.4
99-136-6	07/06/1999	phosgene	IBU			RCdL	17.1	2.4	6.1
99-136-6	07/06/1999	phosgene	IBU			LML	35.2	4.1	7.6
99-136-6	07/06/1999	phosgene	IBU			RMR	31.1	4.3	6.2
99-136-6	07/06/1999	phosgene	IBU			LCR	22.4	2.9	6.7
99-136-6	07/06/1999	phosgene	IBU			LCdR	30.6	4.1	6.5
99-136-6	07/06/1999	phosgene	IBU			RAc	9.8	1.1	7.9
99-153-3	07/12/1999	phosgene	IBU	20	20	RCL	14.2	2.3	5.2
99-153-3	07/12/1999	phosgene	IBU			RCdL	35.5	5.5	5.5
99-153-3	07/12/1999	phosgene	IBU			LML	30	4.3	6.0
99-153-3	07/12/1999	phosgene	IBU			RCR	23.6	3.4	5.9
99-153-3	07/12/1999	phosgene	IBU			RCdR	44.1	5.3	7.3
99-153-3	07/12/1999	phosgene	IBU			LMR	31	3.8	7.2
99-153-3	07/12/1999	phosgene	IBU			LAC	12.3	1.7	6.2

	AVG	STD
Wet Wt	12.92857	8.051649
Dry Wt	2.028571	1.263216
W/D R	5.4	0.142511

	AVG	STD
Wet Wt	25.62857	12.35769
Dry Wt	3.757143	1.971342
W/D R	6.0	0.868145

	AVG	STD
Wet Wt	21.17143	11.27811
Dry Wt	3.428571	1.882121
W/D R	5.2	0.202233

	AVG	STD
Wet Wt	30.84286	16.34899
Dry Wt	4.285714	2.416215
W/D R	6.4	0.451374

	AVG	STD
Wet Wt	34.28571	23.20283
Dry Wt	4.414286	3.010774
W/D R	6.8	0.241209

	AVG	STD
Wet Wt	20.24286	7.493299
Dry Wt	2.642857	1.111841
W/D R	6.9	1.071067

	AVG	STD
Wet Wt	19.14286	10.53025
Dry Wt	3.157143	1.779379
W/D R	5.1	0.187191

	AVG	STD
Wet Wt	26.67143	12.88354
Dry Wt	3.328571	1.552111
W/D R	6.9	0.515187

	AVG	STD
Wet Wt	24.71429	8.90214
Dry Wt	3.157143	1.151603
W/D R	6.9	0.704672

	AVG	STD
Wet Wt	27.24286	11.40714
Dry Wt	3.757143	1.425783
W/D R	6.2	0.805968

TABLE E. 5.

Animal #	Date exposed	Exposure Phos/Air	Treatment	weight kg	weight kg	Lung ID	Wet Wt (gm)	Dry Wt (gm)	(Wet-Dry)/Dry Ratio (gm)
98-213-1	11/23/1998	phosgene	NA	19.1	20	RML	24.5	3.1	6.9
98-213-1	11/23/1998	phosgene	NA			LCL	13.6	1.5	8.1
98-213-1	11/23/1998	phosgene	NA			LCdL	26.3	2.9	8.1
98-213-1	11/23/1998	phosgene	NA			RCR	12.4	2	5.2
98-213-1	11/23/1998	phosgene	NA			RCdR	21.6	3.9	4.5
98-213-1	11/23/1998	phosgene	NA			LMR	21.6	3.2	5.8
98-213-1	11/23/1998	phosgene	NA			LAc	8	1	7.0
98-232-2	12/28/1998	phosgene	NA	18.6	18.6	RCL	19.3	3.3	4.8
98-232-2	12/28/1998	phosgene	NA			RCdL	17.7	3	4.9
98-232-2	12/28/1998	phosgene	NA			LML	26.4	4.6	4.7
98-232-2	12/28/1998	phosgene	NA			RMR	25.6	4.4	4.8
98-232-2	12/28/1998	phosgene	NA			LCR	22.7	3.7	5.1
98-232-2	12/28/1998	phosgene	NA			LCdR	15.3	2.8	4.5
98-232-2	12/28/1998	phosgene	NA			RAc	4.4	0.7	5.3
99-255-3	02/08/1999	phosgene	NA	17.7	17.3	RML	18.6	3	5.2
99-255-3	02/08/1999	phosgene	NA			LCL	15.6	2.2	6.1
99-255-3	02/08/1999	phosgene	NA			LCdL	12.3	2.1	4.9
99-255-3	02/08/1999	phosgene	NA			RCR	12.5	2.1	5.0
99-255-3	02/08/1999	phosgene	NA			RCdR	11.8	2.2	4.4
99-255-3	02/08/1999	phosgene	NA			LMR	24.7	4.1	5.0
99-255-3	02/08/1999	phosgene	NA			LAc	7	1.1	5.4
99-21-2	04/05/1999	phosgene	NA	21	21.8	RCL	19.3	2.5	6.7
99-21-2	04/05/1999	phosgene	NA			RCdL	27.3	4.4	5.2
99-21-2	04/05/1999	phosgene	NA			LML	29.5	3.3	7.9
99-21-2	04/05/1999	phosgene	NA			RMR	25.9	3.8	5.8
99-21-2	04/05/1999	phosgene	NA			LCR	33.7	4.3	6.8
99-21-2	04/05/1999	phosgene	NA			LCdR	31.3	5.4	4.8
99-21-2	04/05/1999	phosgene	NA			RAc	5.3	0.9	4.9
99-92-6	05/10/1999	phosgene	NA	18.6	18.2	RCL	12.4	2.1	4.9
99-92-6	05/10/1999	phosgene	NA			RCdL	20.7	3.6	4.8
99-92-6	05/10/1999	phosgene	NA			LML	22.8	3.7	5.2
99-92-6	05/10/1999	phosgene	NA			RMR	38.7	5.9	5.6
99-92-6	05/10/1999	phosgene	NA			LCR	16.1	2.5	5.4
99-92-6	05/10/1999	phosgene	NA			LCdR	33.7	5.7	4.9
99-92-6	05/10/1999	phosgene	NA			RAc	6.8	1.1	5.2
99-287-2	06/01/1999	phosgene	NA	15	17.3	RML	21.3	2.9	6.3
99-287-2	06/01/1999	phosgene	NA			LCL	13.1	1.9	5.9
99-287-2	06/01/1999	phosgene	NA			LCdL	8.4	1.2	6.0
99-287-2	06/01/1999	phosgene	NA			RCR	12.4	1.9	5.5
99-287-2	06/01/1999	phosgene	NA			RCdR	17.2	2.7	5.4
99-287-2	06/01/1999	phosgene	NA			LMR	27.9	3.8	6.3
99-287-2	06/01/1999	phosgene	NA			LAc	10.6	1.5	6.1
98-241-6	01/12/1999	phosgene	NAC	20.5	20.9	RML	44	5.3	7.3
98-241-6	01/12/1999	phosgene	NAC			LCL	30.9	3.7	7.4
98-241-6	01/12/1999	phosgene	NAC			LCdL	17.3	2.2	6.9
98-241-6	01/12/1999	phosgene	NAC			RCR	24.5	3.2	6.7
98-241-6	01/12/1999	phosgene	NAC			RCdR	17.7	3	4.9
98-241-6	01/12/1999	phosgene	NAC			LMR	39.3	4.9	7.0
98-241-6	01/12/1999	phosgene	NAC			LAc	11.5	1.5	6.7
98-249-1	01/18/1999	phosgene	NAC	20	20	RML	32.9	5.2	5.3
98-249-1	01/18/1999	phosgene	NAC			LCL	19.2	2.5	6.7
98-249-1	01/18/1999	phosgene	NAC			LCdL	12	1.9	5.3
98-249-1	01/18/1999	phosgene	NAC			RMR	58.6	8.3	6.1
98-249-1	01/18/1999	phosgene	NAC			LCR	23.3	3	6.8
98-249-1	01/18/1999	phosgene	NAC			LCdR	36.2	5.5	5.6
98-249-1	01/18/1999	phosgene	NAC			LAc	13.3	2	5.7
99-249-5	01/25/1999	phosgene	NAC	19.1	19.1	RCL	10.6	1.5	6.1
99-249-5	01/25/1999	phosgene	NAC			RCdL	20.7	3.6	4.8
99-249-5	01/25/1999	phosgene	NAC			LML	30.8	4.6	5.7
99-249-5	01/25/1999	phosgene	NAC			RCR	15.7	2.5	5.3
99-249-5	01/25/1999	phosgene	NAC			RCdR	21.5	3.5	5.1
99-249-5	01/25/1999	phosgene	NAC			LMR	24.7	4.2	4.9
99-249-5	01/25/1999	phosgene	NAC			RAc	5.9	1	4.9
98-116-2	11/16/1998	phosgene	PEEP	20	NA	RML	19.8	2.5	6.9
98-116-2	11/16/1998	phosgene	PEEP			LCL	16.9	2.4	6.0
98-116-2	11/16/1998	phosgene	PEEP			LCdL	19.8	2.4	7.3
98-116-2	11/16/1998	phosgene	PEEP			RCR	17.1	2.6	5.6
98-116-2	11/16/1998	phosgene	PEEP			RCdR	19	3	5.3
98-116-2	11/16/1998	phosgene	PEEP			LMR	30	4.3	6.0
98-116-2	11/16/1998	phosgene	PEEP			LAc	4.5	0.5	8.0

	AVG	STD
Wet Wt	18.28571	6.918677
Dry Wt	2.514286	1.038314
W/D R	6.5	1.38014

	AVG	STD
Wet Wt	18.77143	7.530762
Dry Wt	3.214286	1.297984
W/D R	4.9	0.266908

	AVG	STD
Wet Wt	14.64286	5.690594
Dry Wt	2.4	0.930949
W/D R	5.1	0.530223

	AVG	STD
Wet Wt	24.61429	9.671854
Dry Wt	3.514286	1.469046
W/D R	6.0	1.177914

	AVG	STD
Wet Wt	21.6	11.36515
Dry Wt	3.514286	1.79669
W/D R	5.1	0.296274

	AVG	STD
Wet Wt	15.84286	6.822233
Dry Wt	2.271429	0.906852
W/D R	5.9	0.374768

	AVG	STD
Wet Wt	26.45714	12.11416
Dry Wt	3.4	1.36626
W/D R	6.7	0.832286

	AVG	STD
Wet Wt	27.92857	16.32582
Dry Wt	4.057143	2.374066
W/D R	5.9	0.607961

	AVG	STD
Wet Wt	18.55714	8.490751
Dry Wt	2.985714	1.360672
W/D R	5.2	0.480705

	AVG	STD
Wet Wt	18.15714	7.478604
Dry Wt	2.528571	1.119098
W/D R	6.4	0.971506

TABLE E. 5.

Animal #	Date exposed	Exposure Phos/Air	Treatment	weight kg	weight kg	Lung ID	Wet Wt (gm)	Dry Wt (gm)	(Wet-Dry)/Dry Ratio (gm)
98-247-1	01/18/1999	phosgene	PEEP	19.1	19.5	RCL	15.6	2.2	6.1
98-247-1	01/18/1999	phosgene	PEEP			RCdL	33.9	4.9	5.9
98-247-1	01/18/1999	phosgene	PEEP			LML	35.8	5.3	5.8
98-247-1	01/18/1999	phosgene	PEEP			RMR	34.7	5.4	5.4
98-247-1	01/18/1999	phosgene	PEEP			LCR	30.2	3.9	6.7
98-247-1	01/18/1999	phosgene	PEEP			LCdR	43.4	6.7	5.5
98-247-1	01/18/1999	phosgene	PEEP			RAc	12.2	1.5	7.1
99-256-4	02/15/1999	phosgene	PEEP	22.5	23	RML	22.5	3.8	4.9
99-256-4	02/15/1999	phosgene	PEEP			LCL	14.2	2.5	4.7
99-256-4	02/15/1999	phosgene	PEEP			LCdL	10.3	1.8	4.7
99-256-4	02/15/1999	phosgene	PEEP			RCR	13.4	2.3	4.8
99-256-4	02/15/1999	phosgene	PEEP			RCdR	17.5	2.7	5.5
99-256-4	02/15/1999	phosgene	PEEP			LMR	31.9	4.8	5.6
99-256-4	02/15/1999	phosgene	PEEP			LAc	7.7	1.2	5.4
99-259-2	02/22/1999	phosgene	PEEP	19.1	NA	RCL	14.1	2.1	5.7
99-259-2	02/22/1999	phosgene	PEEP			RCdL	20.8	3.7	4.6
99-259-2	02/22/1999	phosgene	PEEP			LML	15.9	2.5	5.4
99-259-2	02/22/1999	phosgene	PEEP			RMR	24.9	4.3	4.8
99-259-2	02/22/1999	phosgene	PEEP			LCR	19	3.3	4.8
99-259-2	02/22/1999	phosgene	PEEP			LCdR	19.2	3.4	4.6
99-259-2	02/22/1999	phosgene	PEEP			RAc	7.6	1.2	5.3

	AVG	STD
Wet Wt	29.4	11.34475
Dry Wt	4.271429	1.858955
W/D R	6.1	0.641946

	AVG	STD
Wet Wt	16.78571	8.209431
Dry Wt	2.728571	1.216161
W/D R	5.1	0.402057

	AVG	STD
Wet Wt	17.35714	5.519317
Dry Wt	2.928571	1.056274
W/D R	5.0	0.430895

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Project Number G1555-48ASTAT (3104)

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WR Rosebrough*
NA Niemuth
C Matthews
J Nagaraja
RMO
* memo only

Date March 13, 2000

To Frances Reid

From Nancy Niemuth

Subject Dose Selection for Phase II of MREF Task 97-48

s:\naga\Task 48\Dose Selection memo.doc

This memo documents the statistical analysis of phosgene (CG) dose – lethality response data collected in Phase I of MREF Task 97-48 in support of dose selection for Phase II experiments.

A probit dose-response model was fitted to the lethality data from 9 CG-exposed animals. Model parameters were used to estimate percentiles of the dose-response curve. Fieller's method could not be used to calculate 95 percent confidence intervals for the percentiles from these data.

Table 1 lists the animals included in the analysis. Table 2 lists estimated percentiles of the dose-response curve. The estimated slope was very steep (17.8). The target dose of 450 mg/m^3 for 10 minutes (4,500 mg min/m^3) selected for Phase II experiments was approximately the LCt_{85}.

Table 1. CG Dose and Lethality Data for MREF Task 97-48, Phase I Animals

Animal ID	CG Concentration (mg/m^3)	Lethality
98-51-3	245	Lived
98-50-7	493	Died
98-55-1	371	Died
98-60-2	329	Lived
98-33-3	377	Lived
98-48-6	557	Died
98-104-6	425	Died
98-18-5	420	Lived
98-116-3	491	Died

Table 2. Selected Percentiles from the Probit Dose Response Curve

Percentile (LCt_{xx})	CG Concentration (mg/m^3)
50	396
60	409
70	424
75	432
80	441
85	453
90	467
95	490

NAN:llj

For Review and Approval

	Name	Internal	Date
Originator	Nancy Niemuth	3/15/00	
Concurrence	Jyothi Nagaraja		
	Claire Matthews	3/15/00	CM
Approved	Bill Rosebrough	WER	3/16/0

ATTACHMENT F

IBUPROFEN PHARMACOKINETICS REPORT

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Lee/Dept. Files
BK Pierce *
NA Niemuth
C Matthews
RMO Files

(* memo only)

(s:\math\G1555\Task 48\IBU_PK-Plasma Report & Memo.Doc)

Date March 14, 2000

To **Frances Reid**

From Claire Matthews/Nancy Niemuth

Subject **Study No. G155548A: Statistical Analyses of Swine/IBU Concentration Data from Pharmacokinetic Studies**

The attached statistical report describes the pharmacokinetic models fitted to plasma ibuprofen concentration data measured in swine experiments conducted under MREF Study No. G155548A.

Please call Claire Matthews at 4-5595 or Nancy Niemuth at 4-3231 if you have any further questions.

MCM/NAN:llj
Attachment

For Review and Approval

	Name	Internal	Date
Originator	Claire Matthews		3/14/00
Originator	Nancy Niemuth		3/14/00
Approved	Ben Pierce		

STUDY NO. G155548A: STATISTICAL ANALYSES OF SWINE/IBU CONCENTRATION DATA FROM PHARMACOKINETIC STUDIES

March 14, 2000

INTRODUCTION

A total of eleven pigs (5 in the air control group and 6 in the phosgene group) were treated with ibuprofen (IBU) in multiple-dosing experiments. Intravenous dosing with IBU was conducted during half-hour infusion periods and was repeated every 2 hours. The first (loading) dose was 45 mg/kg and the following (maintenance) doses were 22.5 mg/kg. Blood draws for plasma IBU measurements were taken at approximately half-hour intervals for most animals.

METHODS

A one-compartment, multiple-dosing pharmacokinetic model was fitted to the plasma IBU concentration data for each animal, using the SAS (V6.12) NLIN procedure. Although a few blood samples were collected during the infusion period, the majority of samples were taken either immediately before or after infusion, or during the elimination phase of the most recent infusion. Therefore, the model was simplified by formulating it as a multiple-dosing series of bolus injections. Each "injection" time was defined as 25 minutes after the start of each dosing period, that is, approximately 5 minutes prior to the first blood draw following the infusion.

A dose interval variable (i) was created to facilitate the model fitting. Animals that survived the entire 24-hour dosing period received a total of 13 doses, so for those animals the dose interval variable ranged from 1 to 13. The number of doses received by animals that died before 24 hours ranged from 4 to 6. The time after dosing (t) for each sample was calculated as the number of hours elapsed since the start of the first infusion. Thus, the pharmacokinetic model for plasma IBU concentration as a function of time t can be stated as follows.

$C_1(t)$ = concentration at time t in dose interval 1 = $2A \exp(-k(t-t_1))$,
where t_1 is the "injection" time for interval 1 and the constant 2 accounts for the first dose being twice as large as the remaining doses;

$C_i(t)$ = concentration at time t in dose interval i ($i \geq 2$)
= $2A \exp(-k(t-t_1)) + A \Sigma \exp(-k(t-t_i))$,
where the sum Σ is taken over dose intervals 2 through i, and
t_i is the "injection" time for interval i.

One animal (99-294-3) was inadvertently given a second dose that was approximately as large as the first dose, so the constant 2 was also factored into the second term of the model for that animal. IBU concentrations that were observed prior to the first infusion were not used in modeling for any animal. Two outliers were not used in modeling: for animal 99-293-2, a very low concentration of 0.05 µg/mL immediately after the 10^{th} dose was considered suspect, since it

occurred where a local peak concentration should have been found. Also, for animal 99-136-6, a high concentration of 77.7 μg/mL occurring halfway between the 3rd and 4th dose was considered suspect. On the other hand, for animal 99-272-4, a concentration of 70.2 μg/mL occurring near the end of the first dosing interval was used in the analyses, even though it was a high outlier. The use of this value did not appear to adversely affect the overall fit of the model for this animal.

For each animal, the pharmacokinetic model estimated two parameters A and k, which are the (maintenance-dose) peak height and elimination rate, respectively. The estimated half-life (hr) of the drug was calculated as 0.693/k (Gibaldi and Perrier, p. 5). The modeled-based Cmax (maximum concentration) was predicted as the peak concentration that would occur immediately after the first dose. The predicted total area under the curve (AUC), from the first dose to the end of the experiment, was calculated from the model equation using the final estimated parameters for each animal. For comparison, empirical AUCs were also calculated using the trapezoidal rule.

Steady-state concentrations appeared to be achieved by the third dosing period. Therefore, the model-based average steady-state concentration was calculated as the predicted area under the curve from the third dosing time to the end of the experiment, divided by the time elapsed (hr) between the third dose and the last observation. For comparison, the average steady-state concentration was also calculated using the trapezoidal area under the curve from the third dose to the last observation.

RESULTS

Table 1 presents a summary of the number of doses given and the estimated model-based parameters A and k for each animal. Table 2 presents a summary of other model-based parameters and empirical parameters for each animal. The third column in Table 2 displays the estimated half-life of the drug based on the model. Columns 4 and 5 display observed and modeled maximum plasma IBU concentrations. Columns 6 and 7 display total areas under the curve calculated both from the model and from the trapezoidal rule. Columns 8 and 9 display average steady-state concentrations calculated both from the model and by the trapezoidal rule.

Estimated half-lives ranged from 0.5 hour -1.4 hours. Model-predicted Cmax values ranged from 80-121 μg/mL. Model-based average steady-state concentrations ranged from 18-36 μg/mL. Areas under the concentration-time curve estimated from the model were comparable to, although generally less than, corresponding trapezoidal areas. A similar pattern was evident in the steady-state values estimated by the model compared to those estimated from the trapezoidal areas.

Table 3 presents means of the parameters shown in Table 2. Means were taken over the air control group, the phosgene group, and both groups combined, using values from all animals and values from 24-hour survivors only. Two-sample t-tests were used to investigate possible group effects upon each of the parameters shown. No group effects were statistically significant ($p<0.05$) when using data from all animals, or from survivors only.

Figures 1-11 contain plots of observed plasma IBU concentrations overlaid with values fitted by the pharmacokinetic model (one plot for each animal). Average steady-state values from

the third dosing interval to the end of the experiment are displayed with a dashed line for those animals that survived 24 hours.

REFERENCE

Gibaldi, M., and Perrier, D., (1982). Pharmacokinetics, Second Edition, Revised and Expanded, Marcel Dekker, Inc., pp 5, 113-144.

Table 1. Summary of Estimated Parameters from Multiple-Dose One-Compartment Pharmacokinetic Model.

Group	Animal	No. of Ibuprofen Doses Given	A (μg/mL)	k	Comments
Air/IBU	99-136-1	13	47.6	0.709	
	99-146-3	13	46.8	1.014	
	99-150-3	5	42.9	0.494	(Animal died after 5th dose)
	99-272-2	13	67.6	1.122	Largest IBU concentration occurred after 2nd dose.
	99-293-2	13	53.1	1.054	Very low IBU concentration of 0.05 μg/mL after 10th dose was not used in statistical analyses; sample probably coagulated.
CG/IBU	99-111-4	13	68.2	1.238	
	99-136-6	4	55.0	0.828	(Animal died after 4th dose.) High IBU concentration of 77.7 μg/mL occurring halfway between 3rd and 4th dose was not used in statistical analyses.
	99-153-3	6	50.4	1.046	(Animal died after 6th dose)
	99-272-3	13	62.1	1.190	
	99-272-4	4	51.1	1.026	(Animal died after 4th dose)
	99-294-3	13	48.1	1.296	Second dose was inadvertently given as large as the first (loading) dose; this was factored into the PK model.

Table 2. Pharmacokinetic Parameters for Individual Animals. Modeled Half-life Values, Cmax, AUC, and Average Steady-State Parameters Using Both Empirical (Trapezoidal Rule) Calculations and Multiple Dosing One-Compartment PK Model.

Group	Animal	Half-life (hr)	Maximum Concentration (µg/mL) [a]		Area under the Curve (µg/mL-hr)		Average Steady- State Concentration (µg/mL) [b]	
			Observed	Modeled	Trapezoidal	Modeled	Trapezoidal	Modeled
Air/IBU	99-136-1	0.98	102.1	87.7	1009.8	919.4	37.6	32.5
	99-146-3	0.68	88.1	83.2	717.5	636.1	26.0	23.1
	99-150-3	1.40	94.5	80.9	456.8	439.1	52.8	36.1
	99-272-2	0.62	154.5	118.7	960.9	840.9	29.4	28.9
	99-293-2	0.66	140.1	94.0	770.7	695.1	27.1	25.2
CG/IBU	99-111-4	0.56	133.5	120.6	881.3	797.1	31.3	27.2
	99-136-6	0.84	102.9	102.6	294.3	275.7	39.8	32.1
	99-153-3	0.66	98.4	90.8	347.9	325.3	26.3	24.3
	99-272-3	0.58	147.4	112.4	811.9	725.3	25.3	25.8
	99-272-4	0.68	104.6	80.4	231.2	236.6	25.1	26.2
	99-294-3	0.53	96.4	101.9	691.3	553.7	24.6	18.4

[a] Both observed and modeled Cmax values occurred immediately after the first dose for all animals except 99-272-2, for which the Cmax occurred immediately after the second dose.

[b] Average steady-state concentrations were based on value observed from immediately after the third dose through the end of the experiment for each animal.

Table 3. Averages of Pharmacokinetic Parameters. Modeled Half-life Values, Cmax, AUC, and Average Steady-State Parameters Using Both Empirical (Trapezoidal Rule) Calculations and Multiple Dosing One-Compartment PK Model.

Animals Included	Group	No. of Animals	Half-life (hr)	Maximum Concentration (μg/mL)		Area under the Curve (μg/mL-hr)		Average Steady-State Concentration (μg/mL)	
				Observed	Modeled	Trapezoidal	Modeled	Trapezoidal	Modeled
All Animals	Air/IBU	5	0.87	115.9	92.9	783.1	706.1	34.6	29.1
	CG/IBU	6	0.64	113.9	101.5	543.0	480.6	28.7	25.6
	Combined	11	0.74	114.8	97.6	652.1	583.1	31.4	27.2
Survivors Only	Air/IBU	4	0.73	121.2	95.9	864.7	772.9	30.0	27.4
	CG/IBU	3	0.56	125.8	111.6	794.8	682.0	27.1	23.8
	Combined	7	0.66	123.2	102.6	834.8	733.9	28.8	25.9

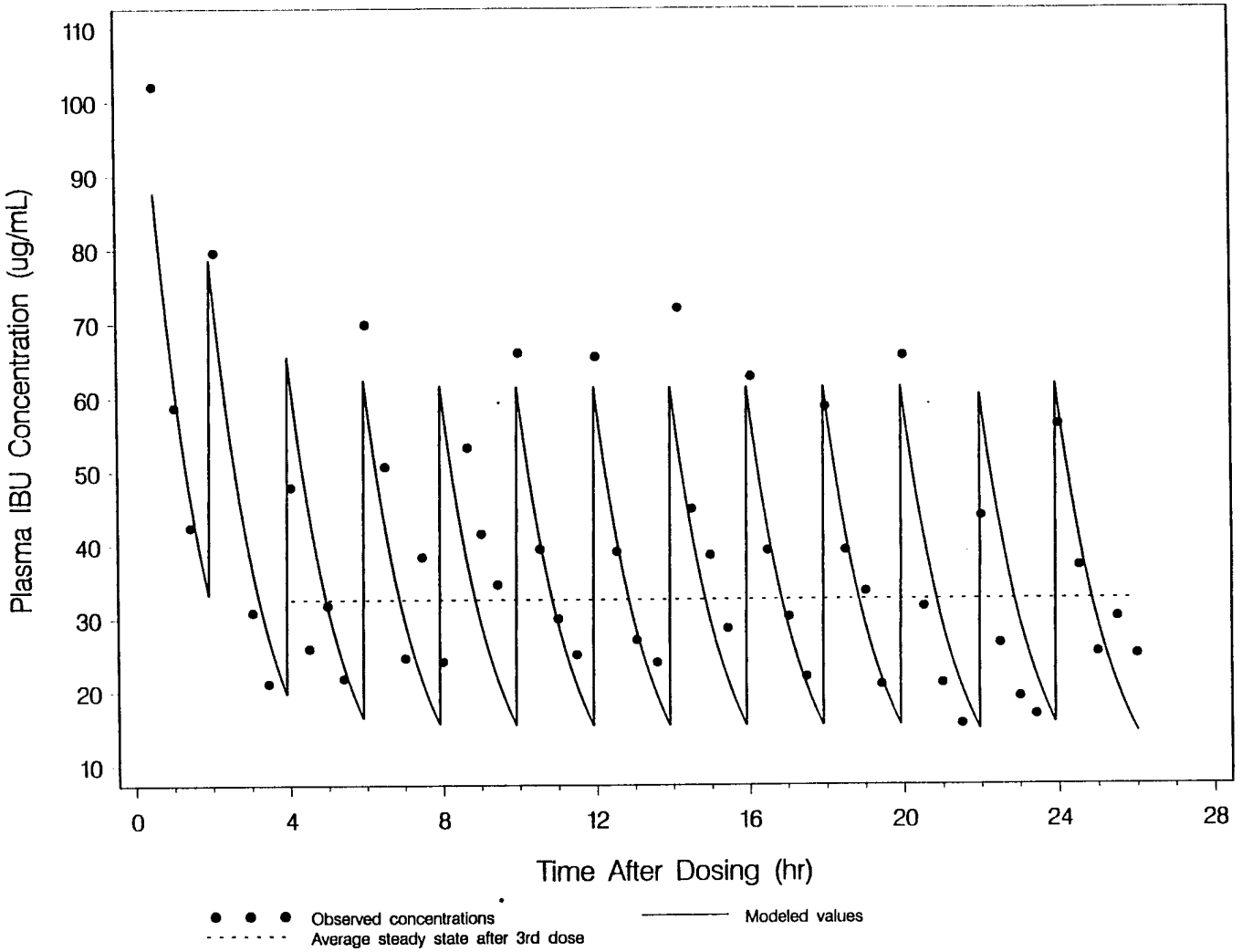

Figure 1. Predicted Plasma IBU Concentrations (μg/mL) Overlaid on Observed Values for Animal 99-136-1 in Air/IBU Compound/Treatment Group.

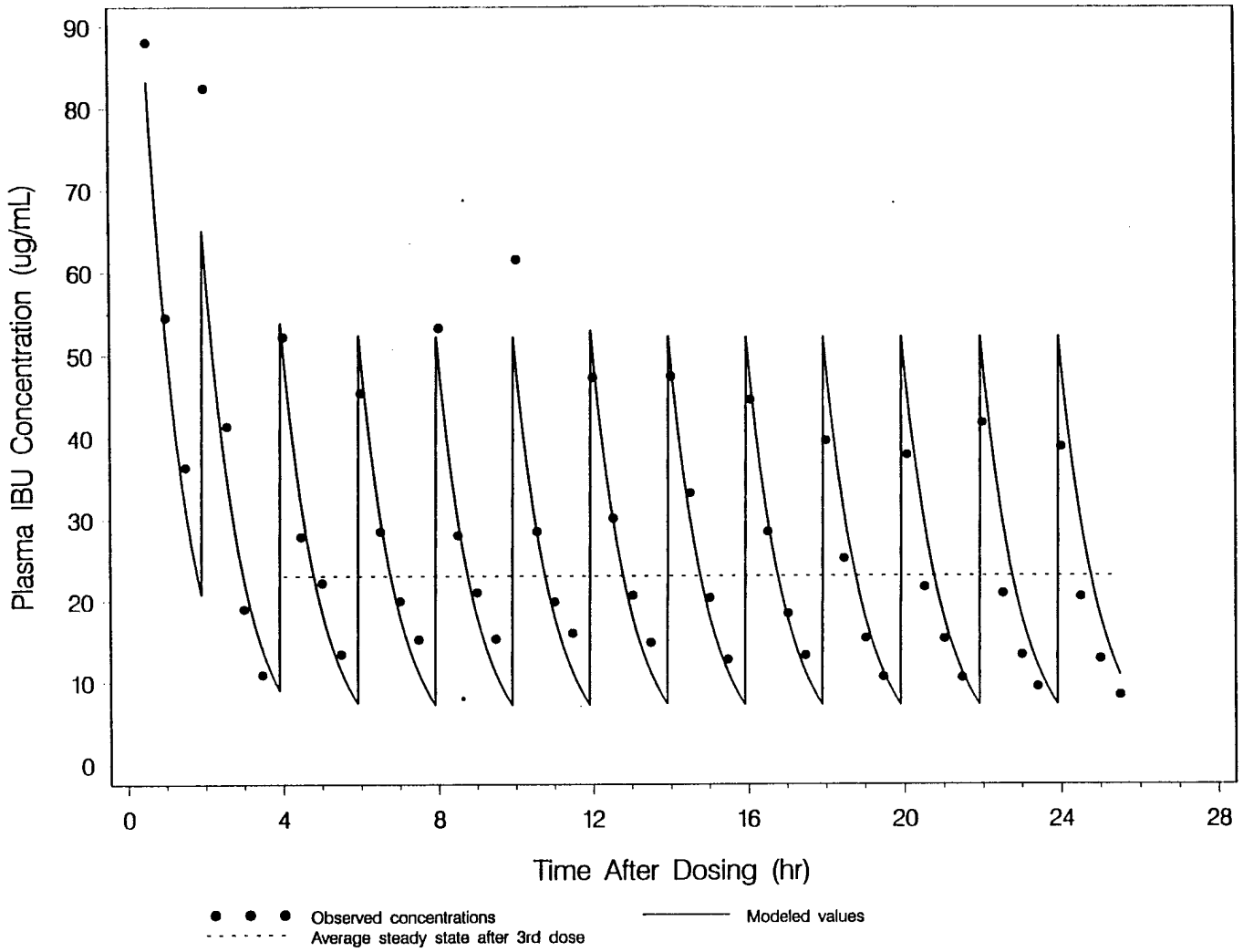

Figure 2. Predicted Plasma IBU Concentrations (μg/mL) Overlaid on Observed Values for Animal 99-146-3 in Air/IBU Compound/Treatment Group.

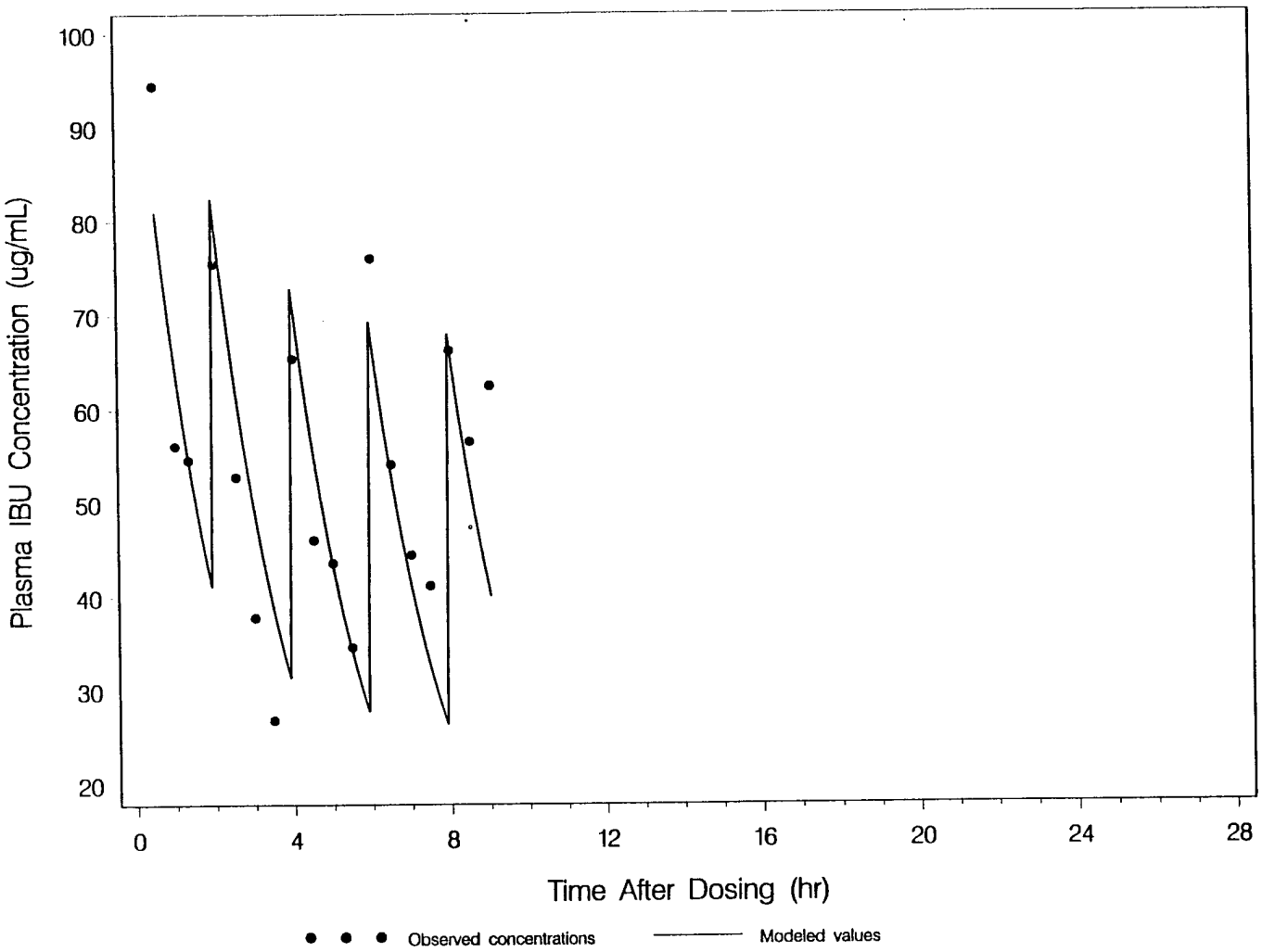

Figure 3. Predicted Plasma IBU Concentrations (μg/mL) Overlaid on Observed Values for Animal 99-150-3 in Air/IBU Compound/Treatment Group.

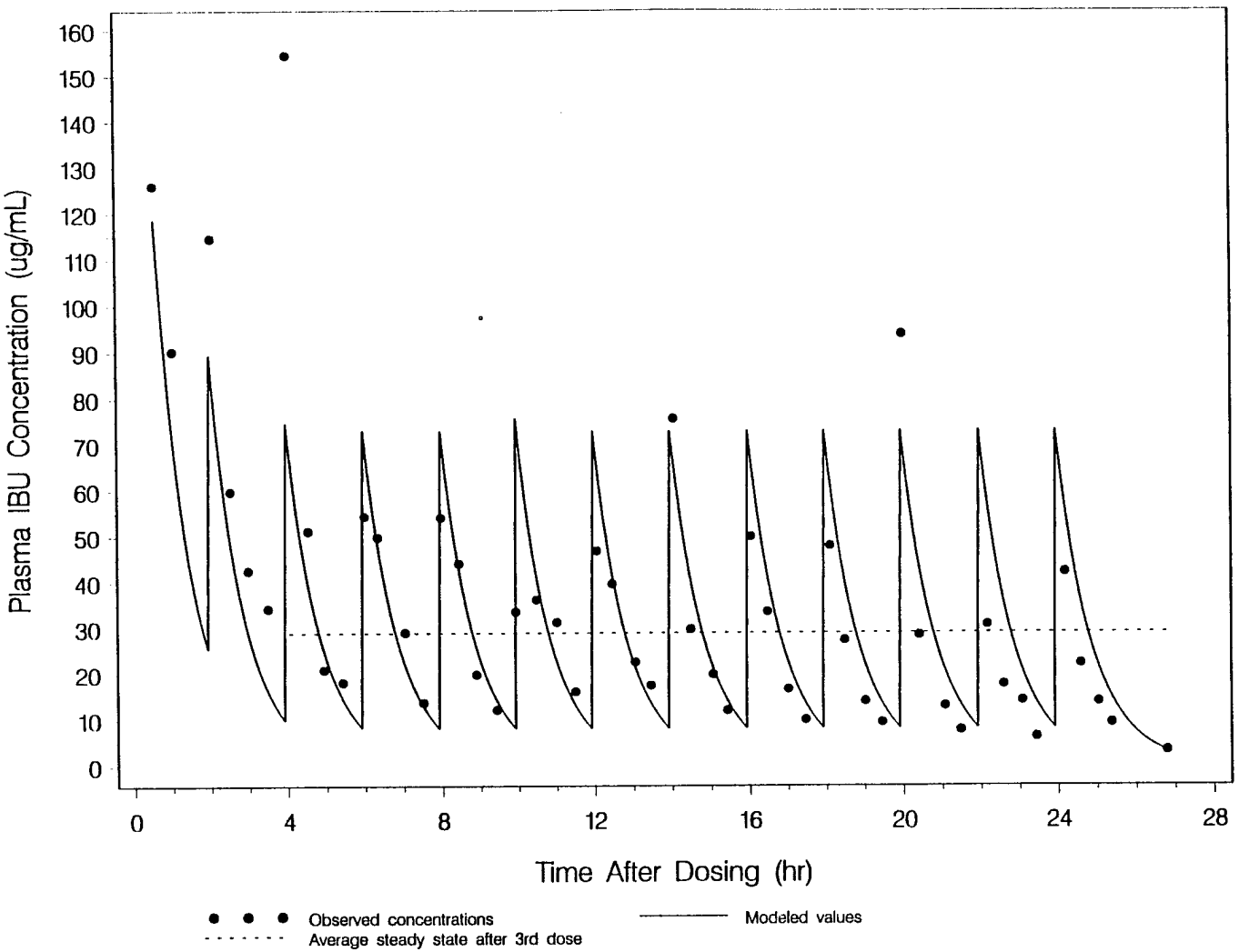

Figure 4. Predicted Plasma IBU Concentrations (μg/mL) Overlaid on Observed Values for Animal 99-272-2 in Air/IBU Compound/Treatment Group.

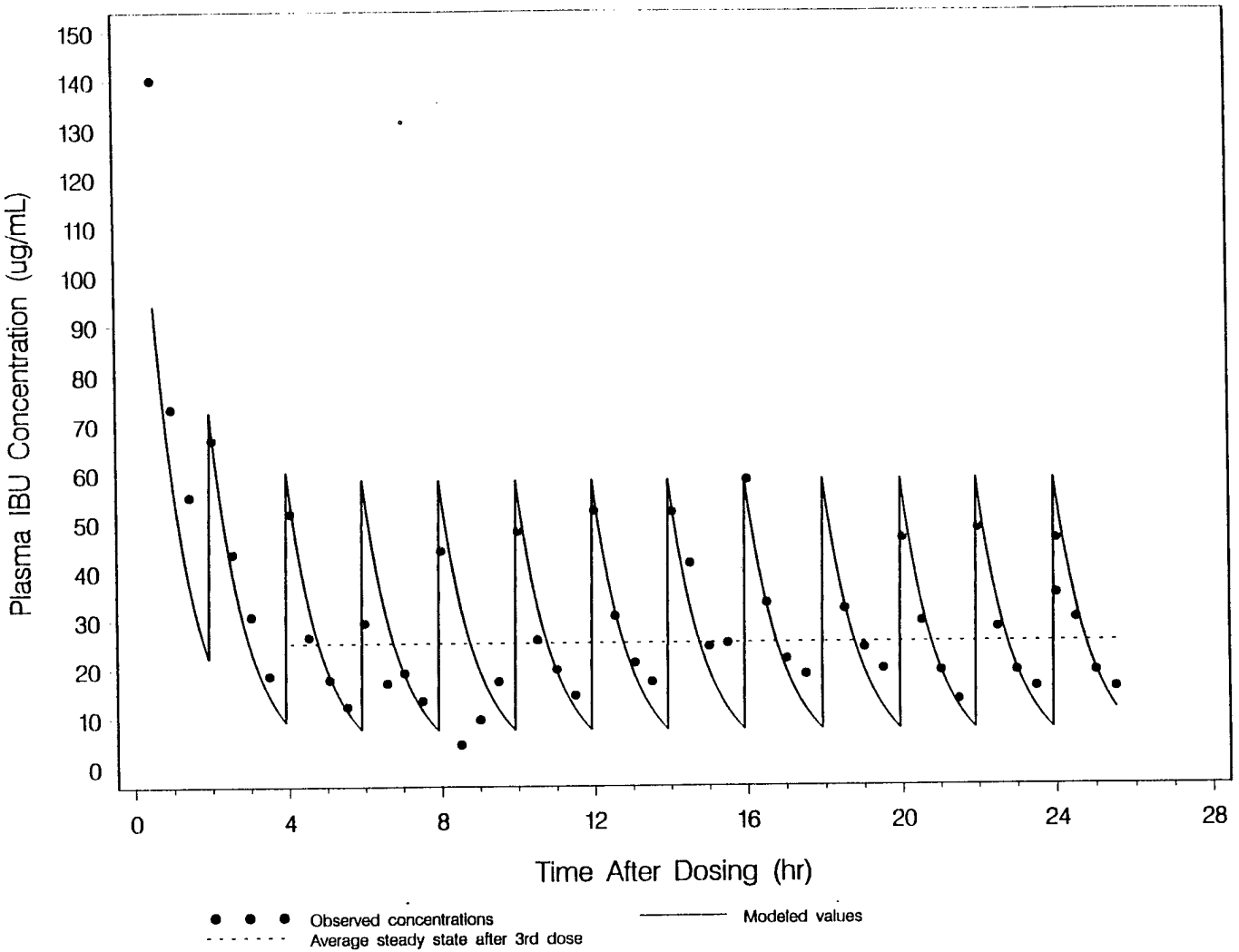

Figure 5. Predicted Plasma IBU Concentrations (μg/mL) Overlaid on Observed Values for Animal 99-293-2 in Air/IBU Compound/Treatment Group.

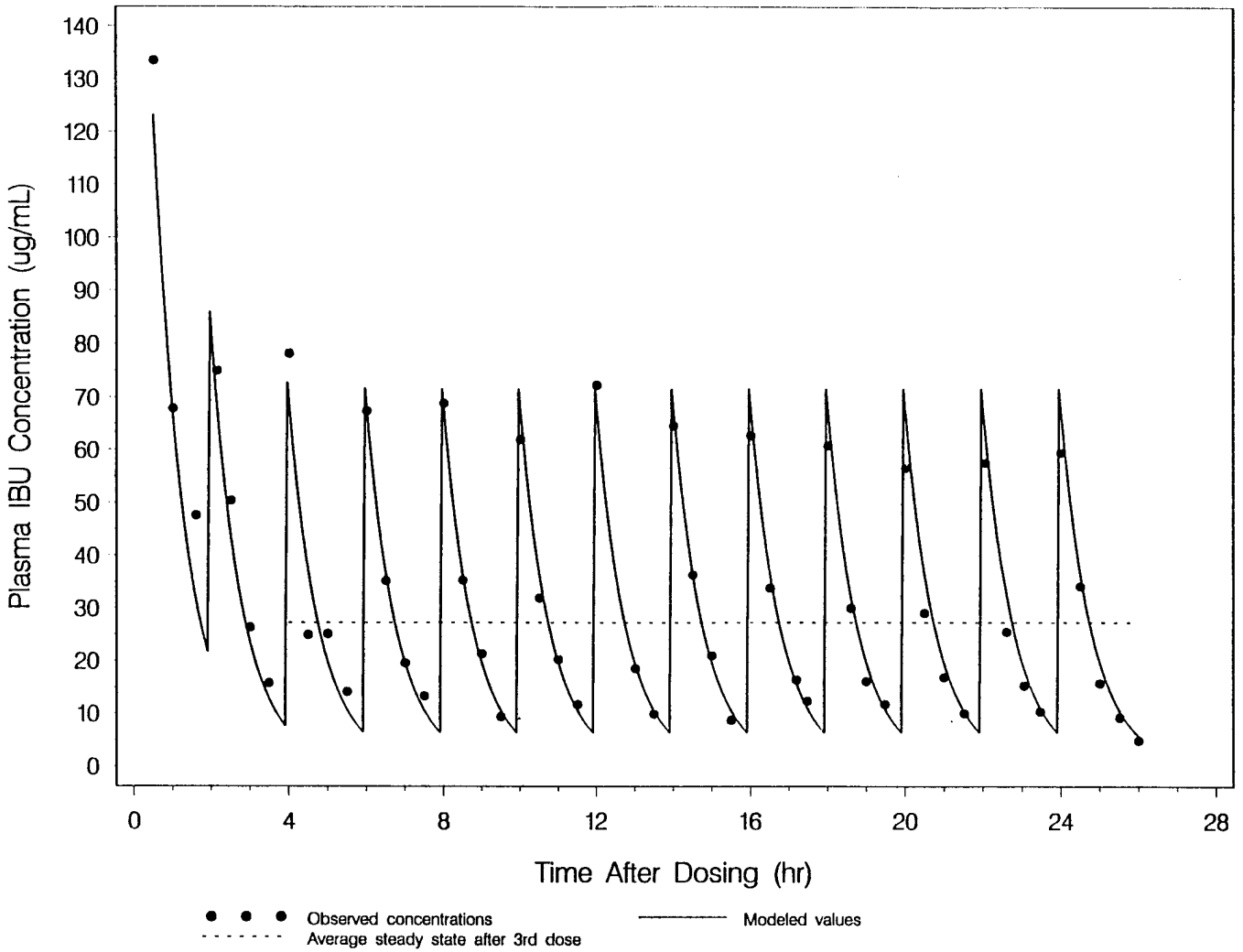

Figure 6. Predicted Plasma IBU Concentrations (μg/mL) Overlaid on Observed Values for Animal 99-111-4 in CG/IBU Compound/Treatment Group.

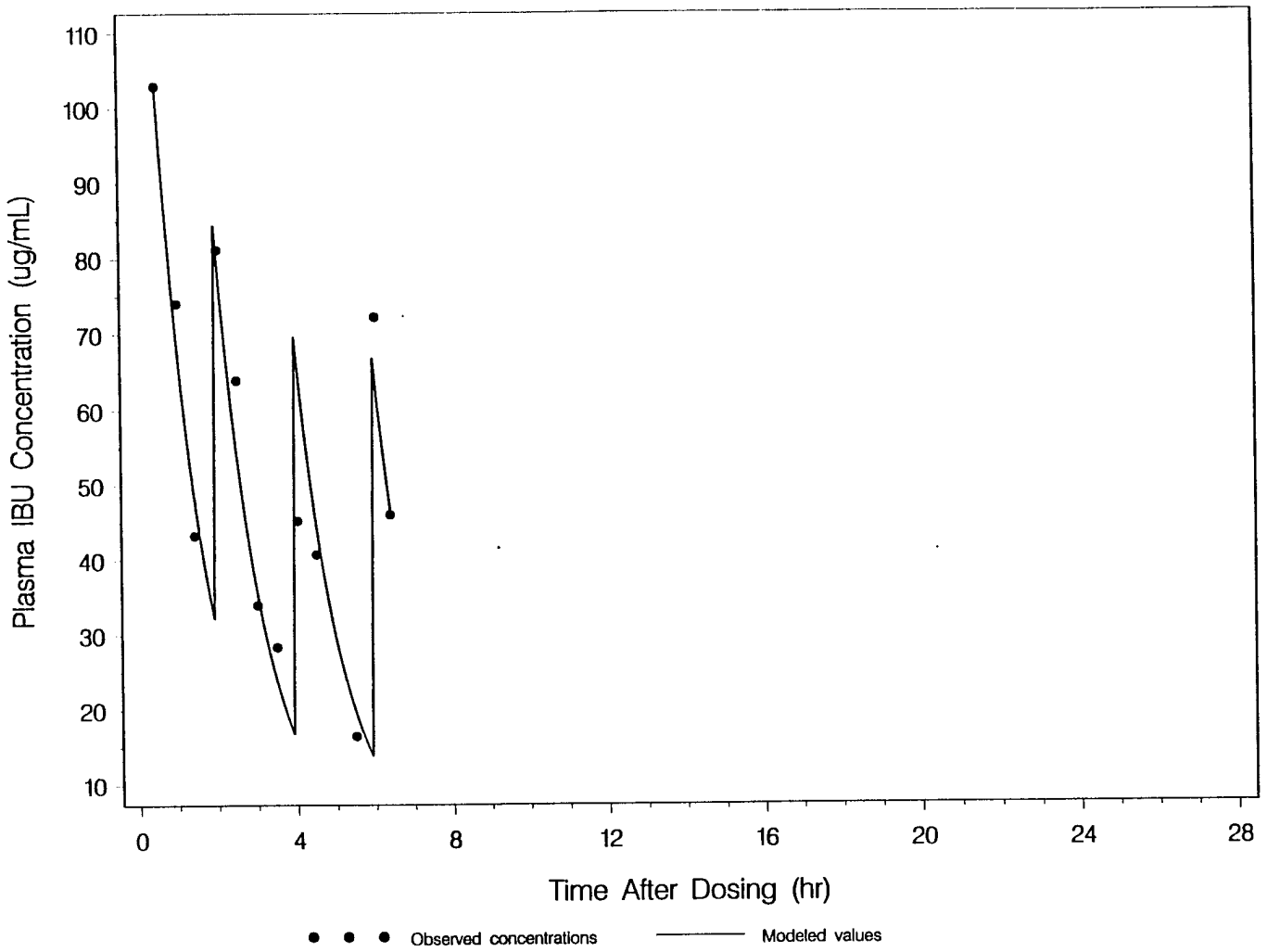

Figure 7. Predicted Plasma IBU Concentrations (μg/mL) Overlaid on Observed Values for Animal 99-136-6 in CG/IBU Compound/Treatment Group.

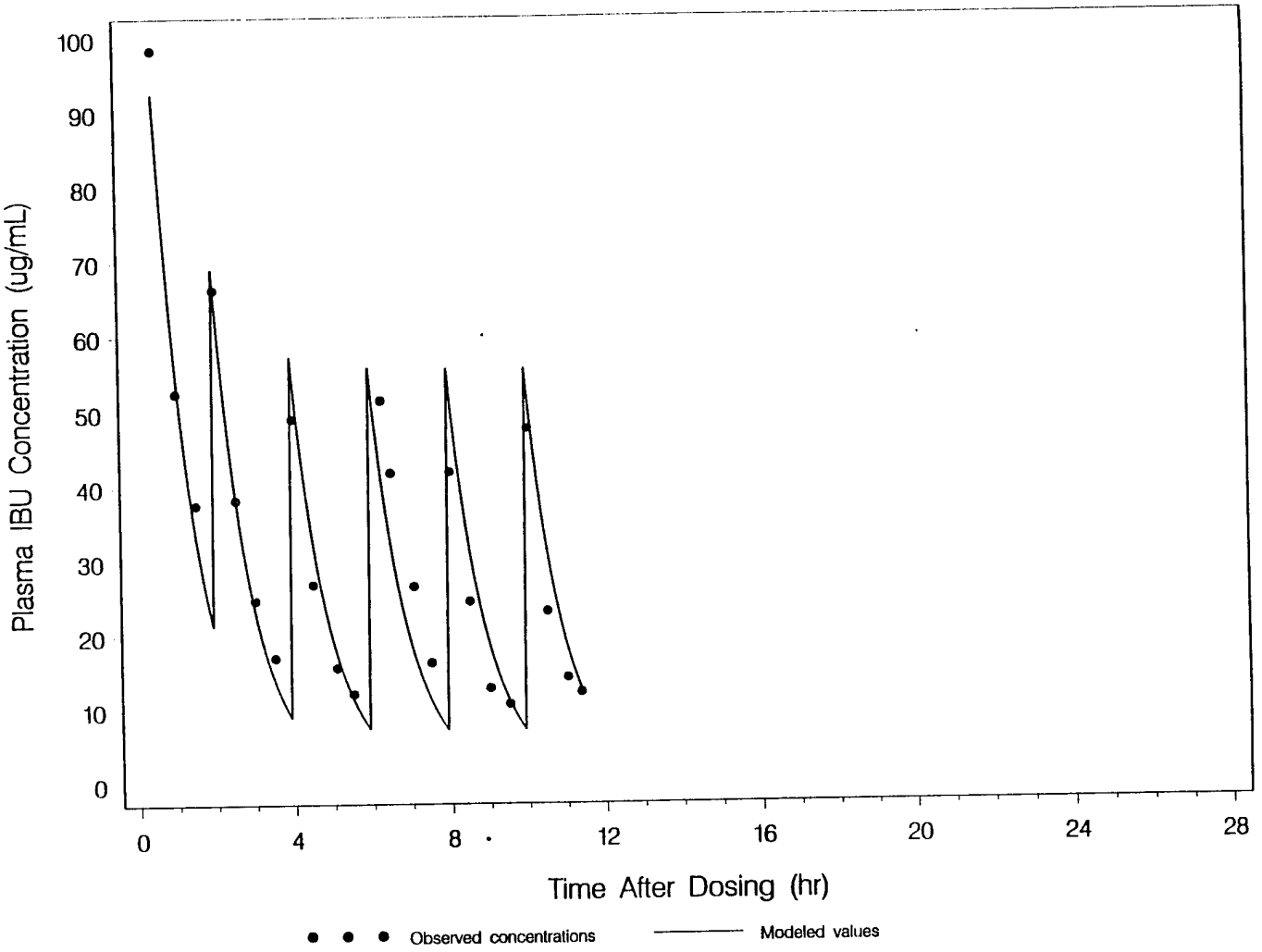

Figure 8. Predicted Plasma IBU Concentrations (μg/mL) Overlaid on Observed Values for Animal 99-153-3 in CG/IBU Compound/Treatment Group.

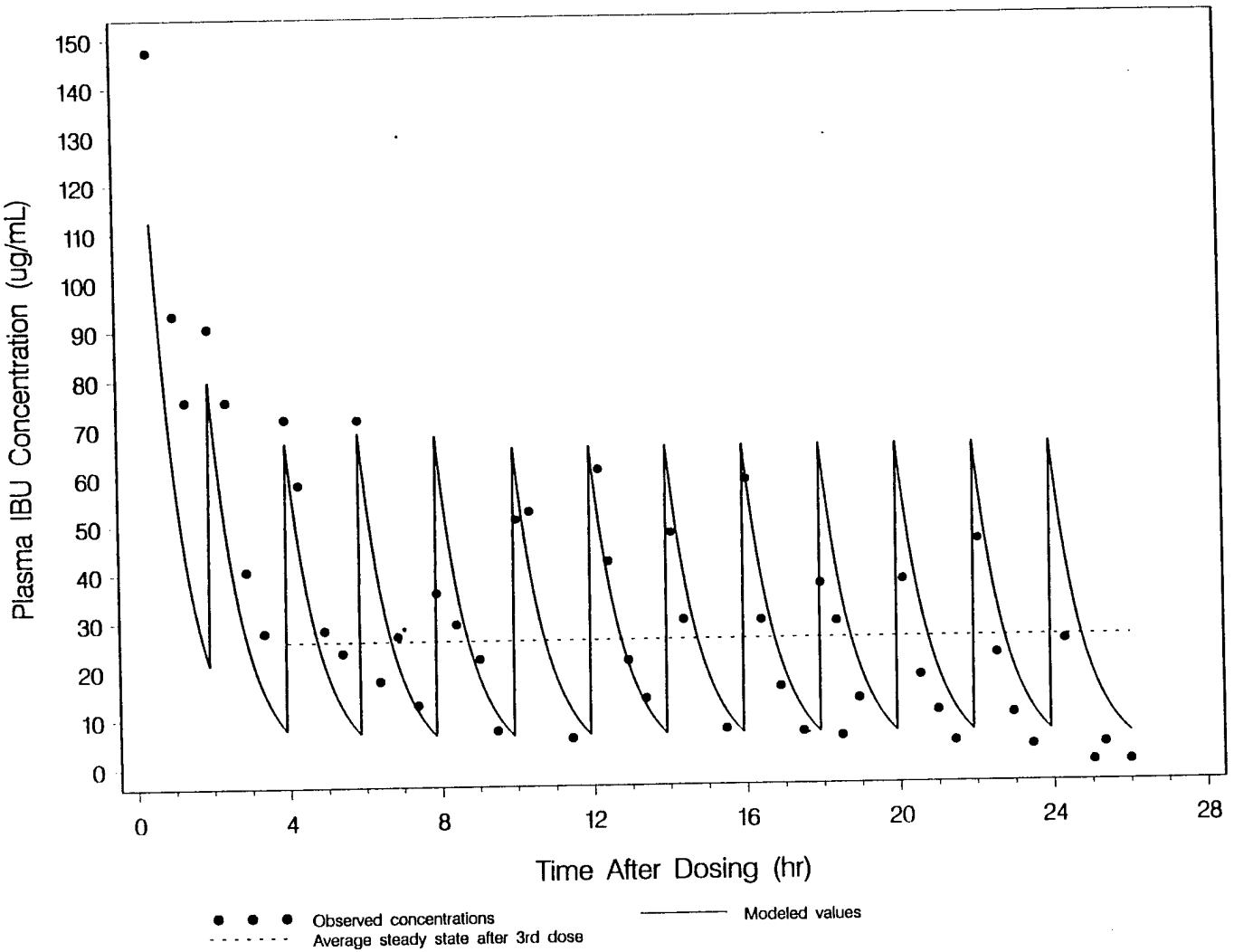

Figure 9. Predicted Plasma IBU Concentrations (μg/mL) Overlaid on Observed Values for Animal 99-272-3 in CG/IBU Compound/Treatment Group.

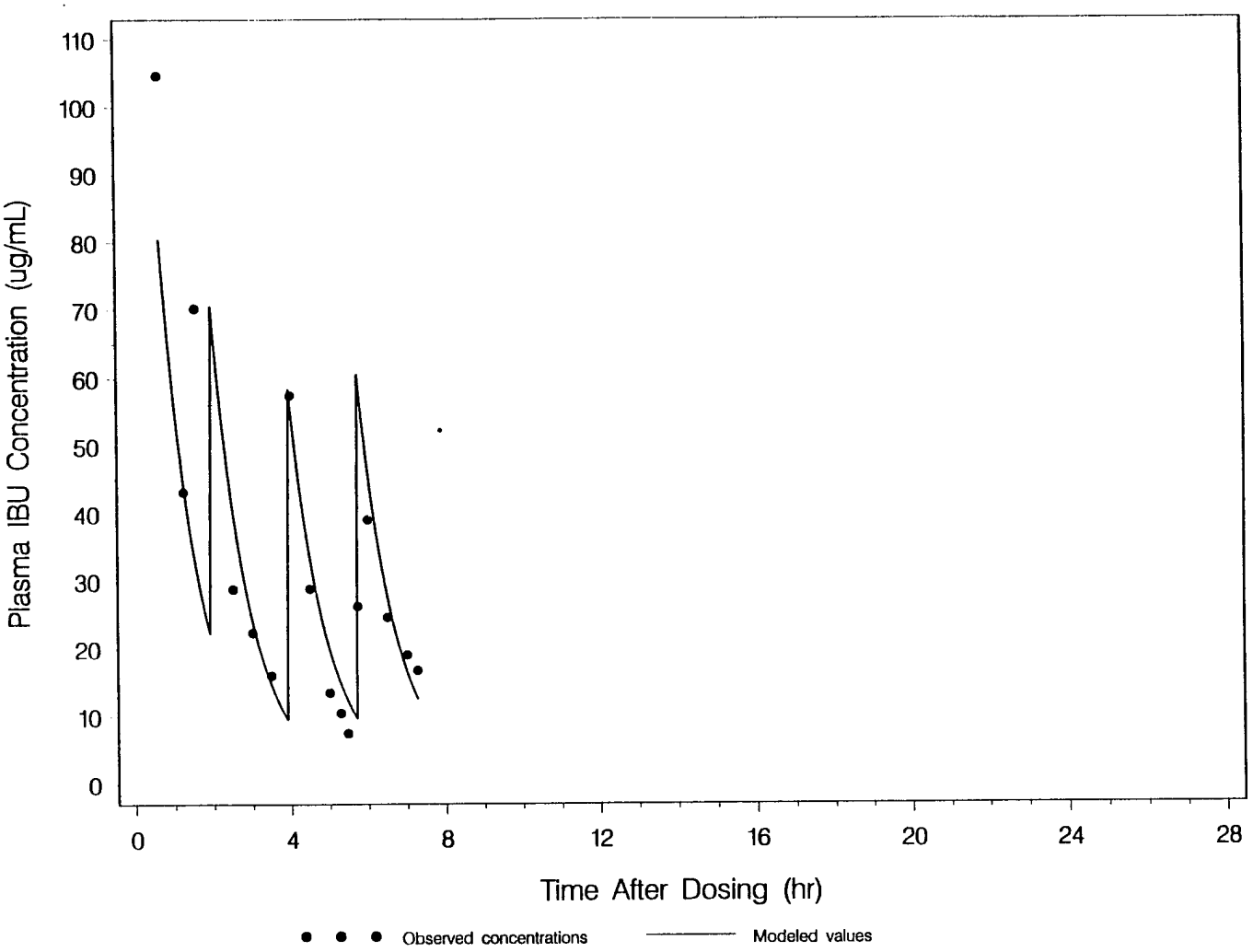

Figure 10. Predicted Plasma IBU Concentrations (μg/mL) Overlaid on Observed Values for Animal 99-272-4 in CG/IBU Compound/Treatment Group.

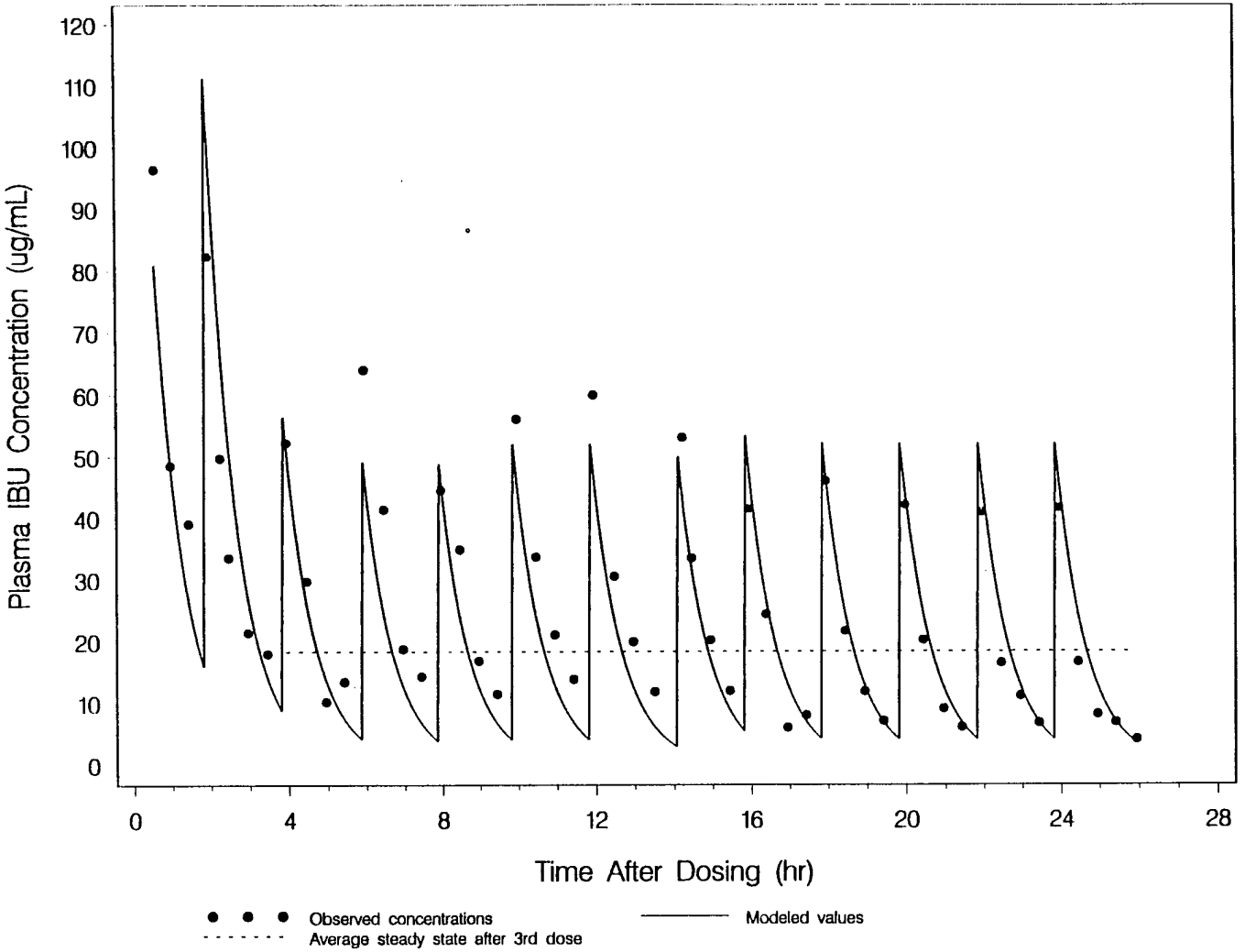

Figure 11. Predicted Plasma IBU Concentrations (μg/mL) Overlaid on Observed Values for Animal 99-294-3 in CG/IBU Compound/Treatment Group.

ATTACHMENT G

CHEMISTRY METHOD FOR DETERMINING IBUPROFEN PLASMA CONCENTRATION AND IBU DOSE PREPARATION AND ANALYSIS SUMMARY REPORT

METHOD FOR QUANTITAVE ANALYSIS Of IBUPROFEN IN WHOLE BLOOD OR PLASMA BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

A. Statement of Work: This method describes the procedures followed for the quantitative analysis of ibuprofen in heparin treated whole blood or plasma. An anticoagulant such as heparin is necessary to allow the separation of the plasma from the red blood cells sample. Sample handling must be conducted using procedures that minimize hemolysis of the blood samples. The use of serum was not evaluated during methods development, but may also be appropriate for this work. Since the sample preparation step of the method initially separates the whole blood into red blood cells and plasma, either starting matrix plasma or whole blood is suitable. Once separated, the plasma is further cleaned and protein precipitated using acidification and a C_{18} solid phase extraction cartridge (SPE). The processed sample is analyzed by high performance liquid chromatography (HPLC). The sample preparation and analysis methods detailed here were developed in support of on-going tasks at the MREF.

Note: The actual instrument IBU calibration range is 200 to 0.25 μg/mL, which is equivalent to 400 to 0.5 μg/mL in the whole blood sample. This dilution factor is a result of using 500 μL of the original 1 mL sample in the extraction process then diluting the extract back to 1 mL for analysis.

B. Equipment: Freezer, centrifuge, centrifuge tubes, latex gloves, laboratory coat, safety glasses, spatula, syringes, Vacuum Manifold for SPE, pipettors and tips, vacuum pump, HPLC analytical system with UV detector and data system, data system autosampler vials, beakers, volumetric flasks, pipettes, pipette bulbs, labels, marking pens,

Equivalent equipment may be substituted for the above listed components.

C. Materials: Heparin treated blood, Ibuprofen sodium salt (Sigma cat# I-4883), dibasic sodium phosphate (Na_2HPO_4) (JT Baker cat# 3818-1), monobasic sodium phosphate ($NaH_2PO_4 \bullet H_2O$) (JT Baker cat# 1-3828), C_{18} solid phase extraction cartridges, concentrated hydrochloric acid, C_{18} analytical column and guard column, Spectroscopic grade acetonitrile (ACN), and Spectroscopic grade water.

D. Area Set Up: A laboratory area with a chemical fume hood for the preparation of the samples and reagents, and an analytical balance used to weigh calibration materials. All materials for sample preparation should be located in or near the hood area

E. Reagent Preparation:

1. **Mobile Phase Buffer**: Accurately weigh 4.26 ± 0.02 g dibasic sodium phosphate and 4.14 ± 0.02 g monobasic sodium phosphate separately on weighing paper. Quantitatively

transfer the powder into a 2-L volumetric flask containing approximately 1 L of HPLC grade water. Mix until dissolved then dilute to a volume of 2-L with HPLC grade water. Then adjust the pH to $7.0_{\pm}0.1$ and filter through a 0.45 um nylon filter. Transfer this solution to a suitable sized container, and label appropriately. This solution can be stored at room temperature for at least a month.

2. **SPE Conditioning Buffer**: Accurately weigh $8.28_{\pm}0.02$ g monobasic sodium phosphate separately onto weighing paper. Quantitatively transfer the powder into a 2-L volumetric flask containing approximately 1 L of HPLC grade water. Mix until dissolved then dilute to a volume of 2-L with HPLC grade water. Then adjust pH to $2.0_{\pm}0.1$ and filter through a 0.45 um nylon filter. Transfer this solution to a suitable sized container, and label appropriately. This solution can be stored at room temperature for at least a month.

3. **Sample Extraction Solution**: The sample extraction buffer is prepared by mixing $400_{\pm}2$ mL of the mobile phase buffer prepared in Section E.1 with $600_{\pm}2$ mL of acetonitrile (ACN). Transfer this solution to a suitable sized container, and label appropriately. This solution can be stored at room temperature for at least a month.

4. **Mobile Phase**: The mobile phase is prepared either by mixing the mobile phase buffer prepared in Section E.1 with acetonitrile in the ratio specified in Section I.1.c or by setting the HPLC gradient system to perform the mixing.

5. **Dilute Hydrochloric Acid Solution**: Add $10_{\pm}0.1$ mL of concentrated hydrochloric acid to a 100-mL volumetric flask containing ~50 mL of HPLC grade water. Mix the solution well, then bring to volume with HPLC water re-mix. Transfer this solution to a suitable sized container, and label appropriately. This solution can be stored at room temperature for at least a month.

F. Preparation of the Blood Samples Extracted as Standards: **Note:** The IBU stock solution is prepared from IBU sodium salt. The FW of IBU equals 206.3 g/mole. The FW of sodium salt + 2 H_2O = 264.3 g/mole. Since the sodium salt is used, the correction for the salt and water must be made. This correction equals 206.3/264.3 = 0.781. The Standards should be prepared in a range of concentrations, which bracket the nominal concentrations of the samples. The method has been found to be linear over the range of 0.25 to 400 μg/mL. An example of a suitable dilution scheme follows

1. 10.0-mg/mL IBU High Level Stock Solution: Into a 100-mL volumetric flask weigh out $1.31_{\pm}0.01$ g of IBU sodium salt, add approximately 50 mL HPLC water to the flask and vortex to mix until dissolved. Then dilute to volume with HPLC water and re-mix solution. Transfer this solution to a suitable sized container, and label with the solution identification (typically laboratory record book number- page number – line number), the

actual calculated concentration (e.g., 10.0 mg/mL), the preparation and expiration dates, storage condition, and the initials of the preparer. This solution can be stored at room temperature for at least a month.

(1.31 g X 0.781)/100 mL = 10.2 mg/mL IBU solution.

2. 1.00-mg/mL IBU Low Level Stock Solution: Into a 100-mL volumetric flask weigh out 0.131 ± 0.01 g of IBU, add approximately 50 mL HPLC water to the flask and vortex to mix until dissolved. Then dilute to volume with HPLC water and re-mix solution. Transfer this solution to a suitable sized container, and label with the solution identification (typically laboratory record book number- page number – line number), the actual calculated concentration (e.g., 1.02 mg/mL), the preparation and expiration dates, and the initials of the preparer. This solution can be stored at room temperature for at least a month.

(0.131 g X 0.781)/100 mL = 1.02 mg/mL IBU solution.

3. 0.100-mg/mL IBU Low Level Stock Solution: Into a 10-mL volumetric flask add approximately 5 mL HPLC water. Add 1.0 ± 0.01 mL of the mid level stock solution prepared in F.2 and vortex to mix. Then dilute to volume with HPLC water and re-mix solution. Transfer this solution to a suitable sized container, and label with the solution identification (typically laboratory record book number- page number – line number), the actual calculated concentration (e.g., 0.100 mg/mL), the preparation and expiration dates, and the initials of the preparer. This solution can be stored at room temperature for at least a month.

(1mL x 1.02 mg/mL)/10 mL = 0.102 mg/mL IBU solution

G. Preparation of Blood for calibration Standards: The analytical standards are extracted from whole blood using the procedures described in Section H. The blood used for this work should be from the same species and free of IBU background or chromatographic interferences. The initial step involves spiking a measured volume of blood (typically 1 mL) with known amounts of IBU. Following the spiking process, the tubes are gently mixed by inversion trying to avoid disruption of the red blood cells. The second step involves processing this standard following the same process used for the samples. The concentration listed for the standards relates to the 1 mL of blood following the procedure. This differs from the analyzed concentration by a factor of two.

All sample tubes must be labeled prior to preparation of the solutions due to the number of manipulations of the samples etc. It is also recommended that the labeling process be supported using a numbered laboratory record book, since the small centrifuge tubes have very limited writing space.

1. 400-µg/mL Analytical Standard: Aliquot 1.00 ±0.01 mL of whole blood into a 1.5-ml microcentrifuge tube. The blood is spiked with 40 µL of the high level stock solution prepared in Section F.1. The tube is mixed gently by inversion for approximately 30 seconds. Collection and Storage of Samples: Samples are collected in GC autosampler vials and stored in the freezer at approximately -20 C pending analysis.

2. 200-µg/mL Analytical Standard: Aliquot 1.00 ±0.01 mL of whole blood into a 1.5-ml microcentrifuge tube. The blood is spiked with 20 µL of the high level stock solution prepared in Section F.1. The tube is mixed gently by inversion for approximately 30 seconds. Collection and Storage of Samples: Samples are collected in GC autosampler vials and stored in the freezer at -20 C pending analysis.

3. 100-µg/mL Analytical Standard: Aliquot 1.00 ±0.01 mL of whole blood into a 1.5-ml microcentrifuge tube. The blood is spiked with 10 µL of the high level stock solution prepared in Section F.1. The tube is mixed gently by inversion for approximately 30 seconds. Collection and Storage of Samples: Samples are collected in GC autosampler vials and stored in the freezer at -20 C pending analysis

4. 50-µg/mL Analytical Standard: Aliquot 1.00 ±0.01 mL of whole blood into a 1.5-mL microcentrifuge tube. The blood is spiked with 5 µL of the high level stock solution prepared in Section F.1. The tube is mixed gently by inversion for approximately 30 seconds. Collection and Storage of Samples: Samples are collected in GC autosampler vials and stored in the freezer at -20 C pending analysis

5. 20-µg/mL Analytical Standard: Aliquot 1.00 ±0.01 mL of whole blood into a 1.5-mL microcentrifuge tube. The blood is spiked with 20 µL of the mid level stock solution prepared in Section F.2. The tube is mixed gently by inversion for approximately 30 seconds. Collection and Storage of Samples: Samples are collected in GC autosampler vials and stored in the freezer at -20 C pending analysis

6. 10-µg/mL Analytical Standard: Aliquot 1.00 ±0.01 mL of whole blood into a 1.5-mL microcentrifuge tube. The blood is spiked with 10 µL of the mid level stock solution prepared in Section F.2. The tube is mixed gently by inversion for approximately 30 seconds. Collection and Storage of Samples: Samples are collected in GC autosampler vials and stored in the freezer at -20 C pending analysis

7. 5.0-µg/mL Analytical Standard: Aliquot 1.00 ±0.01 mL of whole blood into a 1.5-mL microcentrifuge tube. The blood is spiked with 5 µL of the mid level stock solution prepared in Section F.2. The tube is mixed gently by inversion for approximately 30 seconds. Collection and Storage of Samples: Samples are collected in GC

autosampler vials and stored in the freezer at -20 C pending analysis

8. 2.5-μg/mL Analytical Standard: Aliquot 1.00 ±0.01 mL of whole blood into a 1.5-ml microcentrifuge tube. The blood is spiked with 25 μL of the low-level stock solution prepared in Section F.3. The tube is mixed gently by inversion for approximately 30 seconds. Collection and Storage of Samples: Samples are collected in GC autosampler vials and stored in the freezer at -20 C pending analysis

9. 1.0-μg/mL Analytical Standard: Aliquot 1.00 ±0.01 mL of whole blood into a 1.5-mL microcentrifuge tube. The blood is spiked with 10 μl of the mid level stock solution prepared in Section F.3. The tube is mixed gently by inversion for approximately 30 seconds. Collection and Storage of Samples: Samples are collected in GC autosampler vials and stored in the freezer at -20 C pending analysis

10. 0.50-μg/mL Analytical Standard: Aliquot 1.00 ±0.01 mL of whole blood into a 1.5 mL microcentrifuge tube. The blood is spiked with 5 μL of the mid level stock solution prepared in Section F.3. The tube is mixed gently by inversion for approximately 30 seconds. Collection and Storage of Samples: Samples are collected in GC autosampler vials and stored in the freezer at -20 C pending analysis

H. Extraction Process for Sample/Standards:

Both the samples and the standards are processed using the following procedures.

1. Following the preparation of the blood samples for calibration standards or collection of the blood sample, the microcentrifuge tubes are centrifuged until the blood cells clearly separate from the plasma. This typically takes 3 min at 11,000 rpms using the Eppendorf centrifuge.

2. Remove a 0.5±0.005-mL aliquot of the plasma layer and place this into a clean, labeled microcentrifuge tube. A 100±1 uL of the dilute hydrochloric acid solution prepared in E.4 is added to the samples to precipitate the proteins and acidify the sample. The tube is mixed by hand inversion and re-centrifuged to pelletize any suspended solids from the solution.

3. Label and prepare one C_{18} SPE cartridge for each of the microcentrifuge tubes using a SPE vacuum manifold with a vacuum pump. This is done by filling the cartridges with ~1-mL aliquot of spectroscopic grade acetonitrile, ensure the flow control valves are turned off. Turn on the vacuum system and slowly (~1 drop per second) pass the acetonitrile through each cartridge discarding all rinse solutions. This is then followed by ~1-mL aliquot of pH 2 extraction buffer prepared per E.2. The C_{18} cartridge flow is stopped leaving the silica bed wet with buffer.

4. Transfer the entire liquid plasma sample prepared in H.2 directly to the wet SPE cartridge using a transfer pipet.

5. Turn on the vacuum pump and slowly (~1 drop per second) pass the sample through the cartridge being careful to stop the flow when the liquid sample reaches the top of the sorbant bed. The eluent is discarded.

6. To each C_{18} cartridge add 200 ± 1 uL of pH 2 extraction buffer prepared per E.2. Slowly (~1 drop per second) pass this solution through the SPE cartridge being careful to stop the flow when the liquid reaches the top of the sorbant bed. The eluent is discarded.

7. Appropriately labeled autosampler vials are placed into the vacuum manifold. Re-assemble the manifold to collect the samples verifying that the flow tubes are clean and directed into the appropriately labeled sample collection vials.

8. Place 1.0 ± 0.001 mL of Sample Extraction Solution prepared in E.3 into each SPE cartridge. Slowly (~1drop per second), pass this solution through the SPE cartridges collecting the aliquot into the autosampler vials. The first part of this sample (~100 uL) may produce a foamy liquid. If this occurs, stop the flow and let the samples set until the foam disappears. Then restart the flow. The samples will typically then remain clear. This sample flow should continue until all liquid is removed from the SPE cartridges.

9. Once all samples have been extracted turn off the vacuum, remove and cap all vials for analysis.

10. The spent SPE cartridges are discarded as waste.

I. Instrument Set-up:

1. Instrument Parameters: The HPLC is prepared for use with the following recommended initial settings. The optimum operating conditions shall be determined by the analyst:

   a. Column - 15 cm x 4.6 mm inside diameter (I.D) C_{18} Column with 5 um partial size, or equivalent. A C_8 Column will also work but the mobile phase will need to be optimized for that column.

   b. Guard Column - Typically 2.0 cm x 4 mm I.D. C_{18} or C_8 Guard Column to match the analytical column or equivalent.

c. Mobile Phase: 70 percent buffer/30 percent acetonitrile.

d. Mobile Phase Flow Rate: ~1.0 mL/min.

e. Injection: 25 µL volume.

f. Detector Integration Wavelength: 224 nm.

g. Ibuprofen elution time ~ 6.5 min

2. Column Conditioning: The column needs to be conditioned by allowing mobile phase to flow through the column for approximately 30-min or until the baseline has stabilized. The conditioning is performed so that the stationary phase can be equilibrated with the mobile phase, producing a homogeneous environment.

J. Calibration of method: Instrument calibration is performed when quantitation of samples is required by injecting 25 uL of each analytical standard prepared. A complete set of calibration standards will be analyzed prior to analysis of samples. Once the regression results of the instrument response to the calibration standards has been checked, the samples are analyzed with at least every sixth sample being a calibration standard which can be used to verify the stability of the instrument. Additional calibration standards can be analyzed following the last sample. All calibration standards analyzed are used to develop a complete calibration curve for quantitation of the samples. Samples that yield responses less than the calibration range will be reported as less than the lower quantitation limit (lowest standard analyzed). Any sample response that exceeds the largest calibration standard will be reported as greater than the upper quantitation limit (highest calibration standard). Any sample analyzed higher than the calibration range must be diluted to within the calibration range and reanalyzed for final reporting.

1. Calculations:

a. The chromatography system is calibrated using extracted external standards. The data are typically analyzed using a regression model from the data system software. The model used will be determined by the operator based upon the observed regression fit parameters.

b. If a regression program is not available, generate the X coefficients, intercept (b), and correlation coefficient for IBU for the calibration data.

c. Enter the peak area of the IBU (y-value) and the corresponding standard concentration as the ordinate (x-value).

d. Enter each data point obtained from the calibration standards and calculate percent relative standard deviation (% RSD) between replicate standards. Do not include the blank in the calibration calculations, as this will weigh the regression toward zero.

e. If a regression program is not available, use the following calculations:

$$b = \frac{[(\Sigma y)(\Sigma x^2)-(\Sigma x)(\Sigma xy)]}{[n(\Sigma x^2)-(\Sigma x)^2]}$$

$$a = \frac{[n(\Sigma xy)-(\Sigma x)(\Sigma y)]}{[n(\Sigma x^2)-(\Sigma x)^2]}$$

$$r = \frac{[n(\Sigma xy)-(\Sigma x)(\Sigma y)]}{[(n(\Sigma x^2)-(\Sigma x)^2)^{1/2}(n\Sigma(y^2)-(\Sigma y)^2)^{1/2}]}$$

Where,

$$y = ax + b$$

a = slope
b = y-intercept
r = correlation coefficient
x = peak area (IBU)
y = concentration of agent in mg/mL
n = number of replicates

f. Identify the analyte in the sample chromatograms; record the peak areas. Using the regression parameters, calculate the measured concentration for each sample using the data system or the appropriate regression formula.

K. Analysis of Samples: Samples and calibration standards are analyzed using the same procedure. At least every sixth analysis should be a calibration standard.

L. Instrument Shutdown: When the instrument is not to be used for extended periods, the system must be shut down following manufacturer's instructions to ensure column life and instrument stability. The column clean-up procedure is followed, and the column is stored with 100 percent acetonitrile wetting the stationary phase.

1. Column Clean up: At the end of each analysis day, the column needs to be flushed to remove contaminants and buffers. Flush the column with 100 % HPLC grade water for 30 min at a flow rate of 1 mL/min followed by a mixture of 33:33:43 acetonitrile, methanol, and water for approximately 15 min at a flow rate of 2-mL per min. Then flush the column with 100% acetonitrile for approximately 15 min at a flow rate of 2 mL/min.

2. Pump Clean up: Prior to shutdown of the system, the pump seals, injector seal, autosampler needle, and injection loop must be flushed with 100% water and then restored to 100% acetonitrile. If this is not conducted, the salts from the buffer will remain in the system causing blockages. This rinsing can be conducted following the manufacturers recommended procedures.

3. Turn the power to all equipment off.

Originated by: Timothy L Hayes — 4/26/99
Timothy L. Hayes, B.A.
Principal Research Scientist
Date

Reviewed by: Jonathon W. Kohne — 4/26/99
Jonathon W. Kohne
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Elisha N. Morrison, M.S.
Senior Quality Assurance Specialist
Date

INTERNAL REPORT

from

Chemistry

on

Project Number G155548A

Dose Preparation and Analysis for Ibuprofen

to

Dr. Frances Reid

March, 2000

by

Mr. Timothy L. Hayes
Mr. Jonathon W. Kohne

Battelle's Medical Research and
Evaluation Facility
505 King Avenue, JM-3
Columbus, Ohio 43201-2693

Introduction

The chemistry group at Battelle's Medical Research and Evaluation Facility (MREF) was tasked by the Study Director to extract and analyze whole blood samples taken from swine dosed with ibuprofen

Experimental

The dilute solutions were analyzed using high performance liquid chromatography (HPLC) with a tunable absorbance detector (TAD). A calibration curve was generated using standards prepared by diluting Ibuprofen (Sigma, cat# I-4883, lot# 26H1368) with acetonitrile (J.T. Baker, lot# L31806) at the approximate concentrations of 2.0, 1.0, 0.5, and 0.2 mg/mL. An Ibuprofen in methanol control sample (Sigma, cat# I0386, lot# 26H9421) at the concentration of 1.01 mg/mL was analyzed with the dose solution samples. The instrumental parameters are listed in Table 1.:

Table 1. Liquid Chromatography and Variable Wavelength Detector Parameters

Liquid Chromatograph:	Waters 600E pump
Data System:	Millennium 32
Detector	Waters 486 Tunable Absorbance Detector
Autosampler:	Waters 715 UltraWisp
Analytical Column:	Supelco LC-1, 25cm x 4.6mm I.D., 5µm particle size
Analysis Conditions	
Mobile phase:	Isocratic- 67% pH 2.5 HPLC water: 34% acetonitrile
Flow Rate	1.5 mL/minute
Detector Wavelength	214 nm
Injection Volume:	5 µL

Results and Discussion

The results for the ibuprofen dose solution analyses can be found in Table 2. The results for the ibuprofen control sample analyses can be found in Table 3.

Table 2. Ibuprofen Dose Solution Analyses

ANALYSIS DATE	PREP DATE	EXPECTED CONC. (g/mL)	MEASURED CONC. (g/mL)	PERCENT of EXPECTED
November 9, 1998	November 9, 1998	0.201	0.183	91%
December 7, 1998	December 7, 1998	0.100	0.091	91%
January 25, 1999	January 25, 1999	0.100	0.108	108%
February 4, 1999	February 1, 1999	0.101	0.098	97%
February 15, 1999	February 15, 1999	0.101	0.106	105%
February 22, 1999	February 22, 1999	0.101	0.099	98%
March 1, 1999	March 1, 1999	0.101	0.100	99%
March 11, 1999	March 8, 1999	0.100	0.091	91%
March 29, 1999	March 29, 1999	0.100	0.094	94%
April 12, 1999	April 12, 1999	0.100	0.090	90%
May 3, 1999	May 3, 1999	0.098	0.084	86%
May 17, 1999	May 17, 1999	0.100	0.088	88%
May 24, 1999	May 24, 1999	0.101	0.087	86%
June 7, 1999	June 7, 1999	0.100	0.087	87%
June 21, 1999	June 18, 1999	0.103	0.086	84%
June 28, 1999	June 28, 1999	0.101	0.096	95%
July 6, 1999	July 5, 1999	0.100	0.113	112%
July 12, 1999	July 12, 1999	0.100	0.103	102%

Table 3. Ibuprofen Control Sample Analyses

ANALYSIS DATE	EXPECTED CONC. (mg/mL)	MEASURED CONC. (mg/mL)	PERCENT of EXPECTED	COMMENT
November 9, 1998	1.01	1.11	110%	Solvent loss is likely.
December 7, 1998	1.01	-0.034	-3%	Note: Insufficient sample volume
January 25, 1999	1.01	1.17	116%	
February 4, 1999	1.01	1.010	100%	
February 15, 1999	1.01	1.02	101%	
February 22, 1999	1.01	1.04	103%	
March 1, 1999	1.01	1.03	102%	
March 11, 1999	1.01	0.964	95%	
March 29, 1999	1.01	0.966	96%	
April 12, 1999	1.01	0.955	95%	
May 3, 1999	1.01	0.891	88%	
May 17, 1999	1.01	0.901	89%	
May 24, 1999	1.01	0.908	90%	
June 7, 1999	1.01	0.903	89%	
June 21, 1999	1.01	0.862	85%	
June 28, 1999	1.01	0.999	99%	
July 6, 1999	1.01	1.04	103%	
July 12, 1999	1.01	1.10	109%	

Conclusion

The data indicates that, each of the diluted samples contained only one integratable peak. Therefore, the chromatographable purity is greater than 99%. The spectra provided can be manually compared to that originally acquired when the material was synthesized for confirmation that the material has not changed.

DOSE CONFIRMATION SUMMARY SHEET FOR IBUPROFEN DOSE SOLUTIONS G1555-48A

IBUPROFEN DOSE PREPERATION ANALYSIS DATA

ANALYSIS DATE	PREP DATE	EXPECTED CONC. (g/mL)	MEASURED CONC. (g/mL)	PERCENT of EXPECTED
November 9, 1998	November 9, 1998	0.201	0.183	91%
December 7, 1998	December 7, 1998	0.100	0.091	91%
January 25, 1999	January 25, 1999	0.100	0.108	108%
February 4, 1999	February 1, 1999	0.101	0.098	97%
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March 1, 1999	March 1, 1999	0.101	0.100	99%
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April 12, 1999	April 12, 1999	0.100	0.090	90%
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May 24, 1999	May 24, 1999	0.101	0.087	86%
June 7, 1999	June 7, 1999	0.100	0.087	87%
June 21, 1999	June 18, 1999	0.103	0.086	84%
June 28, 1999	June 28, 1999	0.101	0.096	95%
July 6, 1999	July 5, 1999	0.100	0.113	112%
July 12, 1999	July 12, 1999	0.100	0.103	102%

DOSE CONFIRMATION SUMMARY SHEET FOR IBUPROFEN DOSE SOLUTIONS G1555-48A

IBUPROFEN CONTROL SAMPLE ANALYSIS DATA

ANALYSIS DATE	EXPECTED CONC. (mg/mL)	MEASURED CONC. (mg/mL)	PERCENT of EXPECTED	COMMENT
November 9, 1998	1.01	1.11	110%	Solvent loss is likely.
December 7, 1998	1.01	-0.034	-3%	Note: Insufficient sample volume
January 25, 1999	1.01	1.17	116%	
February 4, 1999	1.01	1.010	100%	
February 15, 1999	1.01	1.02	101%	
February 22, 1999	1.01	1.04	103%	
March 1, 1999	1.01	1.03	102%	
March 11, 1999	1.01	0.964	95%	
March 29, 1999	1.01	0.966	96%	
April 12, 1999	1.01	0.955	95%	
May 3, 1999	1.01	0.891	88%	
May 17, 1999	1.01	0.901	89%	
May 24, 1999	1.01	0.908	90%	
June 7, 1999	1.01	0.903	89%	
June 21, 1999	1.01	0.862	85%	
June 28, 1999	1.01	0.999	99%	
July 6, 1999	1.01	1.04	103%	
July 12, 1999	1.01	1.10	109%	

ATTACHMENT H

STATISTICAL REPORT FOR PHASE II

Battelle
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Project Number G1555-48ASTAT (3104)

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Date June 30, 2000

To **Frances Reid**

From Nancy Niemuth

Subject **Statistical Report on Task 48, Phase II Experiments — Revised**

Attached is the revised statistical report on Phase II experiments conducted under MREF Task 97-48. This report was revised in response to the sponsor's comments on the Draft Final Report for MREF Task 97-48.

Please call me at 424-3231 if you have any questions regarding the statistical analysis.

NAN:llj
Attachment

For Review and Approval

	Name	Internal	Date
Originator	Nancy Niemuth	N	7/11/00
Concurrence			
Approved	Bill Rosebrough	BKR for	7/11/00

MREF TASK 97-48, PHASE II: STATISTICAL REPORT ON TREATMENT EFFICACY PHASE

June 30, 2000

INTRODUCTION

Phase II of MREF Task 97-48 applied the 72-hour anesthetized, ventilated, swine model developed in Phase I, to assess the efficacy of three treatments for phosgene (CG) exposure. The three treatments evaluated were:

1) **NAC**: 2 ml of a 200 mg N-acetylcystiene (NAC)/ml solution administered intratracheally 30 minutes post-exposure and every 4 hours thereafter for 16 hours;
2) **IBU**: a loading dose of 45 mg ibuprofen (IBU)/kg administered intravenously 30 minutes post-exposure, followed by 22.5 mg IBU/kg every two hours for 24 hours; and
3) **PEEP**: O_2 support increased to 45 percent immediately after exposure, along with incremental increases of 2-3 cm H_2O positive end expiratory pressure (PEEP) every 30 minutes until the targeted level of 15 cm H_2O PEEP was reached and maintained until end of study.

Animals were exposed by inhalation to either clean air for 10 minutes, or to a targeted 450 mg CG/m^3 for 10 minutes (4,500 mg min/m^3), which was estimated to be the LCt_{85} for CG. A total of 32 swine were allocated to seven exposure/treatment groups in the study, as shown in the table below.

Exposure/ Treatment Group	Animal IDs	Survived/N	Average Survival Time (Hr)
Air/None	98-110-2, 98-236-6, 99-21-1, 99-251-6, 99-287-1, and 99-288-4	6/6	72
Air/IBU	99-136-1, 99-146-3, 99-150-3, 99-272-2, and 99-293-2	3/5	50.54
Air/NAC	98-241-1 and 99-253-1	2/2	72
CG/None	98-213-1, 98-232-2, 99-21-2, 99-255-3, 99-287-2, and 99-92-6	1/6	24.90
CG/IBU	99-111-4, 99-136-6, 99-153-3, 99-272-3, 99-272-4, and 99-294-3	2/6	33.05
CG/NAC	98-241-6, 98-249-1, and 99-249-5	1/3	29.64
CG/PEEP	98-116-2, 98-247-1, 99-256-4, and 99-259-2	1/4	24.18

Animals were monitored 24 hours a day for 72 hours for respiratory, clinical chemistry, and hematology parameters. The parameters were measured immediately after exposure and thereafter approximately every hour for respiratory parameters and approximately every four hours for clinical chemistry and hematology parameters throughout the 72-hour study period. Survival time and lung wet and dry weights were also recorded.

For analysis purposes, timecourse designations were defined as follows. The measurement immediately after exposure was taken as time 0 for all parameters of interest. Thereafter, for respiratory parameters timecourse periods were defined for every hour of the 72-hour study period. Each reading was assigned to the nearest timecourse period. For blood chemistry and hematology parameters timecourse periods were defined at 1, 2, 4, 8, 12 hours, etc. The 1 hour timecourse included any readings taken in the first hour following the measurement at time 0. The 2-hour timecourse included any readings taken in the second hour following the measurement at time 0. Later timecourses included readings taken within ±2 hours of the labeled time. When multiple readings were taken within a timecourse period, the average was calculated for use in the statistical analysis.

The clinical chemistry and hematology parameters evaluated in Phase II experiments were sodium (Na), potassium (K), chloride (Cl), blood urea nitrogen (BUN), glucose (Glu), arterial blood pH, partial pressure of carbon dioxide (P_aCO_2), partial pressure of oxygen (P_aO_2), bicarbonate ion (HCO_3), total carbon dioxide (TCO_2), oxygen saturation (SO_2), base excess (BE), anion gap (An Gap), hemoglobin (Hb), and hematocrit (HCT). Respiratory parameters evaluated in this experiment were expired CO_2, inspired O_2, oxygen saturation of capillary blood (SpO_2), pulse rate (PR), heart rate (HR), respiratory rate (RR), impedance of thoracic cavity, systolic blood pressure, diastolic blood pressure, and mean blood pressure.

METHODS

A discriminant analysis procedure was used to select respiratory, clinical chemistry, and hematology parameters that explained the greatest variability between exposure/treatment groups and were also physiologically plausible. The primary variables considered in the discriminant analysis were summary statistics derived from the measured parameters after exploratory analyses and are listed in the table below. For parameters where a clear peak or trend was evident in visual examination of individual animal or group mean timecourse plots, summary statistics were defined to capture that information (e.g., peak BUN, time to peak BUN, slope of chloride vs. time). For other parameters, the average of readings obtained in the first 24 hr and the overall average were calculated. Additional variables considered were time to death, an indicator of whether the animal survived or died, the last timecourse during which blood chemistry and hematology parameters were recorded, and the last timecourse during which respiratory gas parameters were recorded. The SAS STEPDISC procedure was used to select variables in a stepwise approach to the discriminant analysis, wherein the variable that had the greatest discriminating power at each stage was added to the model and subsequent variables were evaluated given the variables already selected. After the addition of each variable, the set of variables selected was assessed to determine whether any could be removed. Several

exploratory models, which included subsets of the data, were fitted. The final model included all groups.

Parameter	Summary Statistics
Clinical Chemistry and Hematology Parameters	
Na	Overall average and average over first 24 hours
K	Peak K before 48 hours and time to Peak
BUN	Peak BUN and time to Peak
Glu	Overall average and average over first 24 hours
Cl	Slope of chloride versus time*
Arterial blood pH	Minimum pH and time to minimum pH
SO_2	Minimum SO_2 and time to minimum SO_2
P_aCO2	Overall average and average over first 24 hours
P_aO_2	
HCO_3	
TCO_2	
BE	
An Gap	
HCT	
Respiratory Gas Parameters	
Expired CO_2	Overall average and average over first 24 hours
Inspired O_2	
Systolic Blood Pressure	
Diastolic Blood Pressure	
Mean Blood Pressure	
RR	
PR	Peak pulse rate, overall average, and average over first 24 hours
HR	Peak heart rate, overall average, and average over first 24 hours
SpO_2	Overall average, average over 24 hours, minimum SpO_2, and time to minimum SpO_2
Impedance	Slope of impedance versus time greater than 4 hours*

* The SAS REG procedure was used to estimate slopes for Cl and impedance.

For each variable selected by the discriminant analysis procedure, along with a small number of variables selected by the study director, an analysis of variance (ANOVA) model was fitted to determine whether significant differences between groups were present. Pairwise comparisons among groups were made using the Tukey-Kramer method, a multiple comparisons procedure that controls the experimentwise error rate. The SAS MIXED procedure was used for these comparisons.

In addition, for each selected parameter, a repeated measures ANOVA model was fitted to the recorded values during the early study period (through 8 hours). This model was used to detect early indicators of treatment effects. Several animals that died before 8 hours or had substantial missing data in the early study period could not be included in the repeated measures analysis. For the analysis of respiratory parameters, animals 99-111-4 and 99-294-3 in the CG/IBU group, animal 99-249-5 in the CG/NAC group, and animals 99-259-2 and 99-256-4 in the CG/PEEP group were not included. For the analysis of blood chemistry and hematology parameters, animals 99-136-6 in the CG/IBU group and 99-249-5 in the CG/NAC group were not included. Also, for respiratory parameters, the 8-hour reading was unavailable for some animals. In these cases, the 9-hour reading was substituted to avoid missing observations in the repeated measures analysis. For the analysis of clinical chemistry and hematology parameters, the 1-hour and 2-hour timecourse designations were combined. The repeated measures ANOVA model was fitted separately for each selected parameter and included as factors in the treatment/exposure group, study timecourse, and their interaction. Within animal variability was modeled as a random effect. The repeated measures models were fitted using the SAS MIXED procedure.

Linear regression models were fitted to the impedance cardiograph readings over time for each animal using the SAS REG procedure. An ANOVA model was fitted to the estimated slopes to determine whether impedance was affected by the treatment regimens. The ANOVA model included as factors the exposure/treatment group, an indicator of whether the animal survived or died, and their interaction. The ANOVA model was fitted using the SAS MIXED procedure. In addition, an F-test was used to compare the estimated slope variances between animals that died and those that survived 72 hours.

Fisher's exact tests were used to compare survival rates between groups. In addition, log rank tests were used to compare the probability of survival over time between groups.

RESULTS

Summary tables displaying the number of observations (N), mean, and standard error for each timecourse period and exposure/treatment group are presented in Tables A1a, A1b, and A1c in Appendix A, for clinical chemistry and hematology parameters. Note that Na levels in all study groups increased initially and then stabilized in surviving animals at a level slightly greater than baseline, but within the normal range for this parameter. Standard errors for BUN and Glu were high, indicating that animal-to-animal variability was large. In the CG/IBU and Air/IBU groups, there was some evidence that glucose levels declined when BUN levels were elevated above the normal range during the first 24 hours on study. A steady increase in Cl levels was observed over 72 hours in all groups.

Tables A2a and A2b of Appendix A present the corresponding summary statistics for respiratory parameters. Standard errors for heart rate, pulse rate, and systolic blood pressure were high indicating large animal-to-animal variability. Also, systolic blood pressure readings in the CG/IBU group appeared to be greater than those of the other groups.

The key variables identified as explanatory variables in the stepwise discriminant analysis were: peak potassium level, peak BUN within the first 48 hours, slope of chloride versus time, average inspired oxygen during the first 24 hours, average P_aO_2 during the first 24 hours, and overall average pulse rate. Average expired CO_2 during the first 24 hours was included in the analysis, as it was identified in exploratory, though not the final, model. In addition, overall average glucose, average Na during the first 24 hours, and average P_aCO_2 during the first 24 hours were analyzed, as the study director had indicated these may be important parameters. Box plots for these variables are displayed in Appendix B, Figures B-1 through B-10, for the seven exposure/ treatment groups. In addition, timecourse plots of group mean scores with associated standard error bars are displayed in Appendix C, Figures C-1 through C-10. In these latter figures, four sets of exposure/treatment groups were plotted to facilitate comparisons between treatment and appropriate control groups and among the treatment groups in CG-exposed animals. Within each figure, timecourse plots for the CG/None, CG/IBU, Air/None, and Air/IBU are overlaid in the upper left hand corner; CG/None, CG/NAC, Air/None, and Air/NAC are overlaid in the upper right corner; CG/None, CG/PEEP, and Air/None are overlaid on the lower right; and CG/None, CG/IBU, CG/NAC, and CG/PEEP are overlaid in the lower left hand corner.

Overall, the statistical analysis of the variables selected in the discriminant analysis did not indicate that the three treatments were effective. However, significant group effects were found in the ANOVA models fitted to the following parameters: average P_aO_2 during the first 24 hours ($p<0.0001$), peak potassium level ($p=0.0027$), peak BUN within the first 48 hours($p=0.0025$), expired CO_2 during the first 24 hours ($p=0.0494$), average P_aCO_2 during the first 24 hours ($p=0.0186$), and average inspired oxygen during the first 24 hours ($p<0.0001$). Comparisons of group means using the Tukey-Kramer method are summarized below and illustrated in the boxplots displayed in Appendix B.

- The mean P_aO_2 during the first 24 hours (Figure B-2) in the CG/PEEP group was not different from that in the air-exposed groups, which may indicate some efficacy of the O_2 treatment. Mean P_aO_2 during the first 24 hours was depressed in the CG/None, CG/NAC, and CG/IBU groups relative to the air-exposed groups ($p<0.01$ for each comparison), but means were not significantly different from each other in the CG/None, CG/NAC, and CG/IBU groups.

- On average, peak potassium levels (Figure B-3) in the Air/IBU ($p=0.0094$) and CG/PEEP ($p=0.0065$) groups were significantly greater than those in the Air/None control group. These levels were also increased in the CG/None group compared to the Air/None group, but the increase was only marginally significant ($p=0.0996$).

- No significant differences among the group means were observed for the slope of Chloride versus time, but variability appears to have increased in the CG-exposed groups, as illustrated in Figure B-4. In addition, average slopes in the CG/PEEP, CG/IBU, and CG/NAC groups appear to be somewhat greater on average than those of air-exposed control animals and CG-exposed animals that received no treatment, although these differences were not statistically significant.

- No significant differences in the overall average pulse rate were observed among the groups, although the CG/None and CG/IBU mean scores were marginally greater than all other group mean scores (Figure B-5).

- The mean peak BUN within the first 48 hours (Figure B-6) of the Air/IBU group was significantly greater than that in all other groups ($p<0.05$ for each comparison), except the Air/NAC group, where variability was greater. Also, the mean in the CG/None group was similar to that in the Air/None group, indicating that CG exposure had no effect on this variable.

- No significant differences in the overall average glucose levels (Figure B-7) or average Na during the first 24 hours (Figure B-8) were observed among the groups.

- Although a significant group effect was detected for expired CO_2 during the first 24 hours, none of the pairwise comparisons indicated that significant differences existed between groups, when adjusted for multiple comparisons. The CG/IBU mean was marginally greater than the AIR/IBU mean ($p=0.0688$) while lesser differences between the other group means were observed (Figure B-9).

- Mean P_aCO_2 during the first 24 hours was significantly greater in the CG/IBU group compared to the Air/IBU ($p=0.0452$) and Air/None group ($p=0.0391$). Mean P_aCO_2 was elevated to lesser levels in the other CG-exposed groups (Figure B-10).

- The mean inspired O_2 during the first 24 hours was greater in the CG/PEEP group compared to all other groups, while the other groups were not significantly different from each other (Figure B-1). This result was expected, as the PEEP treatment included increased oxygen support, while oxygen support was maintained at a constant level for the other treatments.

The repeated measures analysis was used to detect early indicators of treatment effect. The timecourse variable was statistically significant for K, BUN, P_aO_2, pulse rate, and expired CO_2 ($p<0.0001$ for each) and for P_aCO_2 ($p=0.0178$), which suggests that these variables may be considered early indicators of CG exposure.

The effect of exposure/treatment group was statistically significant for K ($p=0.0107$) and P_aO_2 ($p<0.0001$), although these effects were not necessarily indicative of treatment efficacy. As illustrated in Figure C-3, K levels in the Air/IBU and CG/Peep groups became elevated in the first 8 hours, while the K levels for other parameters remained within the normal range. For P_aO_2 (Figure C-2), average levels for CG-exposed groups were lower than those in air-exposed groups, but the IBU and NAC treatments do not appear to have moderated this effect.

For inspired O_2 (Figure C-1), the group, time, and interaction were all highly significant when the CG/PEEP group was included in the model. When CG/PEEP was removed from the model, the interaction effect remained significant ($p<0.0001$), largely due to the rapid decline in the Air/NAC group and the rapid increase in the CG/NAC group during the early study period. The interaction between exposure/treatment group and study timecourse was statistically

significant for P_aO_2, K, pulse rate, and Expired CO_2 ($p<0.001$ for each), and for BUN ($p=0.0044$) and P_aCO_2 ($p=0.0019$), which indicates that the average value of the response varied inconsistently among the treatments over the early timepoints for these parameters. The group mean plots in Appendix C illustrate these effects.

- For P_aO_2 (Figure C-2), the CG/PEEP levels remained near those of the other groups, while P_aO_2 levels decreased in the other CG-exposed groups in the early study period.

- For K (Figure C-3), the Air/IBU levels were greatly elevated in the early study period, compared to the AIR/None and Air/NAC groups. In addition, the K levels in the CG/PEEP group were elevated compared to the CG/None and CG/NAC groups, although K levels in the CG/None group rose to similar levels by 12 hours.

- For pulse rate (Figure C-5), the levels in the CG-exposed groups began to rise after approximately 4 hours, while the levels remained stable in the air-exposed groups.

- For expired CO_2 (Figure C-9), levels began to rise immediately in the CG-exposed groups, while remaining stable or rising more slowly in the air-exposed groups.

- For BUN (Figure C-6), it appears that levels initially rose in all groups, but rose more rapidly in some groups than others.

- For P_aCO_2 (Figure C-10), levels rose in the CG/IBU group, declined in the air-exposed groups, and fluctuated in theremaining groups during the first 8 hours (Figure C-10).

- No findings were noted for chloride (Figure C-4), glucose (Figure C-7), or Na (Figure C-8).

The linear regression models fitted to the impedance cardiograph readings overlaid on the observed data for each animal are presented in Appendix D. It is evident from these plots that the impedance cardiograph readings in surviving animals generally decreased over time, except for animal 99-272-2 (Air/IBU) whose readings initially declined and then began to rise and animal 98-232-2 (CG/None) whose readings increased over time. The impedance readings displayed no consistent trend among animals that died before 72 hours. While impedance appeared to decline at a more rapid rate for some, rapid increases were observed in others.

ANOVA results indicated that mean impedance slopes did not vary either among the exposure/treatment groups or between animals that survived or died. The variability in slopes was significantly greater ($p<0.0001$) among animals that died.

Analysis of survival data indicated that there was no difference in the proportion of surviving animals in Fisher's exact test comparisons between CG/None and CG-exposed animals that received the IBU, NAC, or PEEP treatments ($p>0.05$ for all comparisons). Survival was greater in the Air/None group than in the CG/None ($p=0.0076$), CG/IBU ($p=0.0303$), and CG/PEEP ($p=0.0333$) groups, but did not differ significantly from the CG/NAC group

(p=0.0833) due to the small sample size for that group. Fisher's exact test could not be used to compare survival rates between the Air/None and Air/NAC groups, as all animals survived in both groups. Two of five animals in the Air/IBU group died, which may indicate the IBU treatment was at or near the maximum tolerated dose. However, the Fisher's exact test comparison of survival rates between the Air/None and Air/IBU groups did not indicate there was a statistically significant difference in survival between these groups (p=0.1818). The difference in survival was not statistically significant in comparisons between the Air/IBU and CG/IBU or the Air/NAC and CG/NAC groups (low sample size for both groups).

Log rank test comparisons of survival probabilities over time were in agreement with the Fisher exact test comparisons above, with the exception that survival probabilities were significantly greater in the Air/None group compared to CG/NAC. The probability of survival over time was greater in the Air/None group than in the CG/None (p=0.0043), CG/IBU (p=0.0183), CG/NAC (p=0.0269) and CG/PEEP (p=0.0124) groups. There was no difference in survival probabilities between CG/None and CG-exposed animals that received the IBU, NAC, or PEEP treatments, Air/IBU and CG/IBU, Air/NAC and CG/NAC, Air/None and Air/NAC, or Air/None and Air/IBU groups (p>0.05 for all comparisons).

CONCLUSIONS

Although limited evidence of treatment efficacy was noted, none of the treatments appeared to be consistently effective in moderating the effects of CG exposure at an approximate LCt_{85} dose. There was evidence to suggest that PEEP treatment mitigated the effect of CG on P_aO_2, due to the increased oxygen support. Greater variability in the slope of impedance versus time was noted among animals that died compared to those that survived, although the effect did not appear to be treatment-related.

The key variables identified in the discriminant analysis were: peak potassium level, peak BUN within the first 48 hours, slope of chloride versus time, average inspired oxygen during the first 24 hours, expired CO_2, average P_aO_2 during the first 24 hours, and overall average pulse rate. Of these, K, BUN, P_aO_2, pulse rate, and expired CO_2 were identified as possible early indicators of the effects of CG exposure.

APPENDIX A: TABLES

Table A1a. Descriptive Statistics for Sodium, Potassium, Chloride, Blood Urea Nitrogen (BUN), and Glucose by Exposure/Treatment Groups and Study Timecourse.

Group	Study Time-course	Sodium (mmol/L)		Potassium (mmol/L)		Chloride (mmol/L)		BUN (mg/dL)		Glucose (mg/dL)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/IBU	0	5	138.20 (0.20)	5	4.36 (0.04)	5	102.60 (0.68)	5	10.80 (1.56)	5	83.20 (14.48)
	1	2	138.50 (0.50)	2	4.05 (0.05)	2	101.00 (0.00)	2	14.00 (2.00)	2	105.50 (23.50)
	2	3	138.67 (0.33)	3	3.90 (0.31)	3	106.00 (3.21)	3	11.00 (1.73)	3	62.67 (4.10)
	4	5	136.60 (0.81)	5	5.76 (0.34)	5	103.80 (0.92)	5	15.80 (1.46)	5	71.60 (11.46)
	8	5	137.07 (1.10)	5	6.49 (0.80)	5	107.87 (0.76)	5	23.40 (2.77)	5	54.40 (14.61)
	12	5	136.40 (1.91)	5	6.50 (0.95)	5	107.00 (1.05)	5	29.40 (2.68)	5	86.00 (5.68)
	16	4	136.08 (1.89)	4	6.15 (1.13)	4	106.50 (1.04)	4	40.75 (4.09)	4	80.00 (8.03)
	20	4	137.00 (1.87)	4	6.23 (1.07)	4	107.25 (1.49)	4	49.75 (5.15)	4	88.00 (14.22)
	24	4	137.75 (1.70)	4	6.00 (0.93)	4	108.75 (1.80)	4	53.25 (6.66)	4	77.00 (13.96)
	28	3	140.67 (1.20)	3	4.50 (0.71)	3	110.33 (2.03)	3	53.00 (9.71)	3	78.33 (2.19)
	32	2	143.50 (2.50)	2	3.30 (0.30)	2	113.00 (1.00)	2	50.00 (2.00)	2	85.00 (7.00)
	36	3	145.67 (1.20)	3	3.47 (0.19)	3	114.33 (3.33)	3	36.33 (7.22)	3	84.00 (9.24)
	40	3	146.33 (1.33)	3	3.63 (0.47)	3	116.00 (3.61)	3	30.00 (6.11)	3	84.00 (9.07)
	44	3	145.33 (0.67)	3	3.90 (0.06)	3	114.00 (0.58)	3	26.33 (3.71)	3	91.33 (10.14)
	48	2	145.00 (1.00)	2	3.85 (0.05)	2	116.50 (0.50)	2	23.00 (2.00)	2	91.50 (11.50)
	52	2	146.00 (1.00)	2	3.95 (0.15)	2	118.00 (2.00)	2	23.00 (2.00)	2	85.00 (14.00)
	56	2	147.25 (2.25)	2	4.18 (0.33)	2	118.75 (0.75)	2	24.75 (6.25)	2	75.50 (8.50)
	60	3	146.33 (1.76)	3	4.33 (0.23)	3	117.00 (0.58)	3	24.67 (6.33)	3	72.33 (6.36)
	64	3	147.00 (1.15)	3	3.97 (0.09)	3	118.67 (1.20)	3	24.00 (6.03)	3	75.00 (8.74)
	68	3	146.67 (0.33)	3	3.87 (0.13)	3	118.00 (0.00)	3	23.00 (7.51)	3	78.00 (8.62)
	72	3	147.00 (1.00)	3	3.83 (0.15)	3	118.67 (0.88)	3	21.33 (6.36)	3	78.00 (12.34)
Air/NAC	0	2	138.50 (2.50)	2	3.85 (0.45)	2	109.50 (0.50)	2	9.00 (2.00)	2	64.00 (29.00)
	1	1	140.00 (n/a)	1	3.70 (n/a)	1	105.00 (n/a)	1	9.00 (n/a)	1	67.00 (n/a)
	2	2	137.50 (1.50)	2	3.65 (0.15)	2	110.50 (0.50)	2	11.00 (0.00)	2	80.50 (10.50)
	4	1	136.00 (n/a)	1	3.90 (n/a)	1	108.00 (n/a)	1	12.00 (n/a)	1	96.00 (n/a)
	8	2	137.50 (0.50)	2	4.50 (0.30)	2	106.00 (4.00)	2	15.50 (2.50)	2	95.00 (2.00)
	12	2	139.50 (2.50)	2	4.20 (0.40)	2	108.50 (4.50)	2	19.50 (4.50)	2	92.00 (3.00)
	16	2	140.00 (1.00)	2	4.10 (0.10)	2	110.00 (4.00)	2	23.00 (7.00)	2	92.00 (3.00)
	20	2	141.00 (2.00)	2	3.90 (0.20)	2	112.50 (0.50)	2	25.00 (12.00)	2	93.00 (5.00)
	24	2	142.50 (1.50)	2	3.85 (0.35)	2	112.00 (4.00)	2	24.50 (12.50)	2	91.50 (9.50)
	28	2	143.00 (4.00)	2	3.45 (0.05)	2	121.00 (4.00)	2	20.50 (12.50)	2	67.50 (4.50)
	32	1	150.00 (n/a)	1	4.20 (n/a)	1	120.00 (n/a)	1	33.00 (n/a)	1	67.00 (n/a)
	36	2	144.50 (3.50)	1	4.90 (n/a)	2	115.50 (3.50)	2	24.00 (12.00)	2	77.00 (14.00)
	40	2	145.00 (4.00)	2	4.60 (0.00)	2	116.00 (5.00)	2	25.00 (14.00)	2	82.50 (9.50)
	44	2	146.00 (5.00)	2	3.85 (0.35)	2	120.50 (2.50)	2	23.00 (14.00)	2	73.00 (0.00)
	48	2	144.50 (4.50)	2	3.65 (0.35)	2	122.50 (2.50)	2	20.00 (12.00)	2	68.00 (0.00)
	52	1	139.00 (n/a)	1	3.40 (n/a)	1	121.00 (n/a)	1	7.00 (n/a)	1	70.00 (n/a)
	56	1	140.50 (n/a)	1	4.10 (n/a)	1	114.50 (n/a)	1	8.50 (n/a)	1	85.00 (n/a)
	60	2	145.00 (5.00)	2	3.95 (0.35)	2	117.00 (5.00)	2	12.00 (5.00)	2	76.50 (11.50)
	64	2	144.00 (4.00)	2	3.85 (0.45)	2	118.00 (6.00)	2	9.50 (2.50)	2	69.00 (11.00)
	68	2	143.00 (4.00)	2	3.75 (0.05)	2	120.50 (1.50)	2	8.00 (3.00)	2	64.50 (11.50)
	72	2	143.00 (3.00)	2	3.70 (0.00)	2	120.00 (2.00)	2	9.00 (4.00)	2	57.50 (15.50)

Table A1a. Descriptive Statistics for Sodium, Potassium, Chloride, Blood Urea Nitrogen (BUN), and Glucose by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Sodium (mmol/L)		Potassium (mmol/L)		Chloride (mmol/L)		BUN (mg/dL)		Glucose (mg/dL)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/None	0	6	139.50 (0.96)	6	3.68 (0.19)	6	107.17 (1.01)	6	9.50 (1.23)	6	76.33 (12.81)
	1	5	138.20 (1.16)	5	3.50 (0.22)	5	108.40 (2.04)	5	10.60 (2.01)	5	74.80 (9.47)
	2	1	139.00 (n/a)	1	4.30 (n/a)	1	108.00 (n/a)	1	10.00 (n/a)	1	83.00 (n/a)
	4	6	137.50 (0.92)	6	4.25 (0.18)	6	106.00 (1.26)	6	13.67 (1.87)	6	94.33 (8.41)
	8	6	138.83 (0.75)	6	3.88 (0.13)	6	107.83 (1.25)	6	18.17 (2.89)	6	95.50 (11.22)
	12	6	138.83 (0.98)	6	3.73 (0.14)	6	106.83 (1.30)	6	21.50 (3.38)	6	92.00 (9.89)
	16	6	138.50 (1.06)	6	3.67 (0.08)	6	109.33 (1.65)	6	21.17 (2.83)	6	92.00 (7.71)
	20	5	139.60 (1.03)	5	3.48 (0.10)	5	111.80 (1.59)	5	19.80 (2.13)	5	89.40 (3.03)
	24	5	139.80 (0.73)	5	3.36 (0.16)	5	113.80 (1.16)	5	18.40 (2.06)	5	82.60 (4.65)
	28	5	141.80 (2.33)	5	3.34 (0.22)	5	113.80 (1.98)	5	16.00 (2.39)	5	75.80 (6.30)
	32	5	141.00 (0.71)	5	4.04 (0.07)	5	109.60 (1.33)	5	18.20 (2.56)	5	91.00 (2.35)
	36	4	142.00 (0.91)	4	3.88 (0.09)	4	111.75 (1.03)	4	17.50 (3.40)	4	92.50 (2.25)
	40	5	141.20 (1.36)	5	3.98 (0.11)	5	112.40 (1.25)	5	15.40 (2.11)	5	89.80 (4.26)
	44	6	141.33 (1.20)	6	3.90 (0.11)	6	113.17 (1.74)	6	17.00 (2.34)	6	83.33 (3.65)
	48	5	141.80 (0.97)	5	3.78 (0.17)	5	115.20 (2.27)	5	14.20 (1.88)	5	76.00 (4.53)
	52	5	140.80 (1.46)	5	3.88 (0.16)	5	114.60 (0.98)	5	13.40 (1.33)	5	76.20 (1.59)
	56	5	141.60 (1.12)	5	3.86 (0.10)	5	112.80 (0.97)	5	13.60 (1.36)	5	82.80 (1.98)
	60	5	141.20 (1.11)	5	3.84 (0.15)	5	112.60 (1.17)	5	13.60 (1.21)	5	82.40 (5.79)
	64	6	142.83 (1.97)	6	3.83 (0.13)	6	117.50 (3.30)	6	13.33 (1.33)	6	76.50 (5.04)
	68	5	141.20 (1.16)	5	3.78 (0.08)	5	114.60 (1.29)	5	11.60 (0.60)	5	74.40 (5.92)
	72	6	141.67 (0.95)	6	3.65 (0.08)	6	116.50 (0.89)	6	11.83 (1.70)	6	69.67 (4.39)
CG/IBU	0	6	139.33 (0.92)	6	4.12 (0.16)	6	105.50 (0.96)	6	9.67 (0.61)	6	89.33 (13.42)
	1	5	138.60 (0.68)	5	4.20 (0.11)	5	104.40 (0.87)	5	10.80 (0.58)	5	84.00 (15.14)
	2	1	138.00 (n/a)	1	4.30 (n/a)	1	104.00 (n/a)	1	12.00 (n/a)	1	98.00 (n/a)
	4	5	139.40 (1.50)	5	5.22 (0.47)	5	107.20 (2.65)	5	13.80 (0.86)	5	90.20 (17.14)
	8	6	139.46 (0.67)	6	5.22 (0.25)	6	108.41 (1.79)	6	20.24 (1.47)	6	116.36 (16.95)
	12	4	138.75 (1.65)	4	5.43 (0.87)	4	108.25 (1.65)	4	27.00 (2.68)	4	116.25 (34.50)
	16	3	138.67 (0.33)	3	4.67 (0.87)	3	106.00 (1.15)	3	31.33 (3.38)	3	102.00 (10.97)
	20	3	140.00 (0.58)	3	4.27 (0.26)	3	105.33 (1.45)	3	32.67 (2.19)	3	92.67 (7.69)
	24	3	141.00 (0.58)	3	4.10 (0.15)	3	107.67 (0.88)	3	30.67 (2.91)	3	86.33 (2.85)
	28	3	142.67 (0.67)	3	5.13 (1.44)	3	111.00 (2.31)	3	27.67 (4.06)	3	80.67 (5.36)
	32	2	145.00 (2.00)	2	3.90 (0.40)	2	110.50 (3.50)	2	20.00 (4.00)	2	106.00 (12.00)
	36	2	147.00 (2.00)	2	3.70 (0.10)	2	111.00 (4.00)	2	17.50 (4.50)	2	103.00 (10.00)
	40	2	147.50 (1.50)	2	3.65 (0.05)	2	114.00 (4.00)	2	16.00 (5.00)	2	97.50 (1.50)
	44	2	146.50 (1.50)	2	3.30 (0.10)	2	115.50 (10.50)	2	14.50 (3.50)	2	95.00 (9.00)
	48	2	147.00 (1.00)	2	3.35 (0.05)	2	116.00 (9.00)	2	14.50 (4.50)	2	93.00 (6.00)
	52	2	148.00 (4.00)	2	3.65 (0.05)	2	112.50 (9.50)	2	16.50 (4.50)	2	106.00 (16.00)
	56	2	148.00 (5.00)	2	3.75 (0.15)	2	112.00 (9.00)	2	15.00 (4.00)	2	103.00 (9.00)
	60	2	146.50 (4.50)	2	3.75 (0.05)	2	114.50 (11.50)	2	14.50 (3.50)	2	107.00 (21.00)
	64	2	147.50 (4.50)	2	4.00 (0.30)	2	114.50 (15.50)	2	14.50 (3.50)	2	82.00 (1.00)
	68	2	147.50 (5.50)	2	3.83 (0.02)	2	115.25 (11.75)	2	14.25 (3.75)	2	93.00 (8.00)
	72	2	147.50 (5.50)	2	4.30 (0.10)	2	113.00 (14.00)	2	15.00 (2.00)	2	95.50 (14.50)

Table A1a. Descriptive Statistics for Sodium, Potassium, Chloride, Blood Urea Nitrogen (BUN), and Glucose by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Sodium (mmol/L)		Potassium (mmol/L)		Chloride (mmol/L)		BUN (mg/dL)		Glucose (mg/dL)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/NAC	0	3	138.00 (0.58)	3	4.10 (0.12)	3	104.33 (1.86)	3	10.00 (1.53)	3	110.00 (3.00)
	1	3	139.00 (0.58)	3	3.70 (0.25)	3	107.00 (2.08)	3	10.67 (1.20)	3	109.00 (4.93)
	4	3	140.83 (3.88)	3	3.97 (1.30)	3	109.33 (6.66)	3	11.00 (1.73)	3	115.67 (30.65)
	8	2	141.00 (2.00)	2	3.75 (0.55)	2	107.00 (4.00)	2	12.50 (2.50)	2	133.50 (32.50)
	12	2	138.50 (0.50)	2	4.25 (0.55)	2	102.50 (1.50)	2	16.00 (3.00)	2	169.50 (51.50)
	16	1	139.00 (n/a)	1	3.60 (n/a)	1	105.00 (n/a)	1	10.00 (n/a)	1	95.00 (n/a)
	20	1	138.00 (n/a)	1	3.30 (n/a)	1	113.00 (n/a)	1	8.00 (n/a)	1	82.00 (n/a)
	24	1	139.00 (n/a)	1	3.70 (n/a)	1	113.00 (n/a)	1	9.00 (n/a)	1	75.00 (n/a)
	28	1	139.00 (n/a)	1	4.20 (n/a)	1	106.00 (n/a)	1	11.00 (n/a)	1	88.00 (n/a)
	32	1	140.00 (n/a)	1	4.00 (n/a)	1	109.00 (n/a)	1	10.00 (n/a)	1	95.00 (n/a)
	36	1	139.00 (n/a)	1	3.60 (n/a)	1	114.00 (n/a)	1	9.00 (n/a)	1	90.00 (n/a)
	40	1	140.00 (n/a)	1	3.50 (n/a)	1	116.00 (n/a)	1	8.00 (n/a)	1	84.00 (n/a)
	44	1	139.00 (n/a)	1	3.50 (n/a)	1	115.00 (n/a)	1	8.00 (n/a)	1	87.00 (n/a)
	48	1	140.00 (n/a)	1	4.00 (n/a)	1	109.00 (n/a)	1	9.00 (n/a)	1	99.00 (n/a)
	52	1	141.00 (n/a)	1	4.20 (n/a)	1	111.00 (n/a)	1	8.00 (n/a)	1	92.00 (n/a)
	56	1	139.00 (n/a)	1	4.00 (n/a)	1	110.00 (n/a)	1	8.00 (n/a)	1	86.00 (n/a)
	60	1	141.00 (n/a)	1	4.30 (n/a)	1	110.00 (n/a)	1	8.00 (n/a)	1	94.00 (n/a)
	64	1	140.00 (n/a)	1	4.10 (n/a)	1	110.00 (n/a)	1	8.00 (n/a)	1	121.00 (n/a)
	68	1	140.00 (n/a)	1	4.20 (n/a)	1	109.00 (n/a)	1	7.00 (n/a)	1	101.00 (n/a)
	72	1	140.00 (n/a)	1	3.60 (n/a)	1	115.00 (n/a)	1	7.00 (n/a)	1	87.00 (n/a)
CG/None	0	6	139.83 (0.48)	6	3.98 (0.10)	6	104.33 (1.12)	6	9.00 (0.58)	6	92.50 (14.66)
	1	5	139.40 (1.44)	5	3.74 (0.02)	5	106.40 (1.40)	5	10.00 (0.71)	5	91.40 (16.19)
	2	1	139.00 (n/a)	1	3.20 (n/a)	1	116.00 (n/a)	1	6.00 (n/a)	1	60.00 (n/a)
	4	6	138.67 (0.80)	6	4.55 (0.25)	6	105.33 (0.95)	6	12.33 (0.49)	6	90.17 (17.75)
	8	6	141.25 (2.86)	6	4.68 (0.78)	6	111.25 (3.12)	6	17.42 (2.29)	6	91.75 (16.64)
	12	5	137.07 (0.90)	5	5.84 (0.98)	5	108.27 (1.81)	5	25.87 (3.36)	5	79.03 (16.96)
	16	3	138.33 (2.33)	3	4.67 (1.17)	3	109.00 (3.06)	3	24.33 (9.39)	3	102.00 (3.00)
	20	2	141.50 (0.50)	2	3.80 (0.00)	2	107.50 (0.50)	2	13.00 (3.00)	2	103.00 (14.00)
	24	2	141.00 (1.00)	2	5.00 (1.10)	2	107.50 (1.50)	2	12.50 (3.50)	2	124.00 (13.00)
	28	1	143.00 (n/a)	1	4.50 (n/a)	1	109.00 (n/a)	1	9.00 (n/a)	1	105.00 (n/a)
	32	1	141.00 (n/a)	1	4.60 (n/a)	1	111.00 (n/a)	1	11.00 (n/a)	1	109.00 (n/a)
	36	1	143.00 (n/a)	1	4.30 (n/a)	1	111.00 (n/a)	1	12.00 (n/a)	1	93.00 (n/a)
	72	1	139.00 (n/a)	1	3.10 (n/a)	1	118.00 (n/a)	1	10.00 (n/a)	1	69.00 (n/a)

Table A1a. Descriptive Statistics for Sodium, Potassium, Chloride, Blood Urea Nitrogen (BUN), and Glucose by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Sodium (mmol/L)		Potassium (mmol/L)		Chloride (mmol/L)		BUN (mg/dL)		Glucose (mg/dL)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/PEEP	0	4	143.25 (4.39)	4	3.60 (0.35)	4	106.75 (4.87)	4	9.75 (1.60)	4	70.25 (18.51)
	1	3	139.00 (0.58)	3	4.17 (0.03)	3	108.67 (1.45)	3	12.67 (2.40)	4	75.50 (16.11)
	4	4	137.13 (1.69)	4	6.45 (0.88)	4	108.25 (3.77)	4	19.25 (3.42)	4	80.25 (20.58)
	8	3	137.00 (1.00)	3	7.10 (1.04)	3	108.67 (2.67)	3	23.67 (3.67)	3	76.33 (28.94)
	12	2	137.50 (0.50)	2	5.40 (0.80)	2	107.00 (0.00)	2	27.00 (5.00)	2	108.50 (6.50)
	16	1	138.00 (n/a)	1	4.40 (n/a)	1	107.00 (n/a)	1	19.00 (n/a)	2	96.00 (17.00)
	20	1	139.00 (n/a)	1	4.30 (n/a)	1	105.00 (n/a)	1	16.00 (n/a)	1	97.00 (n/a)
	24	1	139.00 (n/a)	1	3.80 (n/a)	1	115.00 (n/a)	1	16.00 (n/a)	1	69.00 (n/a)
	28	1	139.00 (n/a)	1	3.90 (n/a)	1	113.00 (n/a)	1	19.00 (n/a)	1	73.00 (n/a)
	32	1	141.00 (n/a)	1	4.40 (n/a)	1	108.00 (n/a)	1	18.00 (n/a)	1	91.00 (n/a)
	36	1	141.00 (n/a)	1	4.10 (n/a)	1	109.00 (n/a)	1	16.00 (n/a)	1	95.00 (n/a)
	40	1	140.00 (n/a)	1	3.60 (n/a)	1	115.00 (n/a)	1	11.00 (n/a)	1	77.00 (n/a)
	44	1	140.00 (n/a)	1	3.60 (n/a)	1	118.00 (n/a)	1	10.00 (n/a)	1	72.00 (n/a)
	48	1	140.00 (n/a)	1	3.80 (n/a)	1	114.00 (n/a)	1	11.00 (n/a)	1	75.00 (n/a)
	52	1	141.00 (n/a)	1	4.00 (n/a)	1	111.00 (n/a)	1	11.00 (n/a)	1	76.00 (n/a)
	56	1	141.00 (n/a)	1	4.20 (n/a)	1	109.00 (n/a)	1	11.00 (n/a)	1	84.00 (n/a)
	60	1	141.00 (n/a)	1	4.30 (n/a)	1	109.00 (n/a)	1	10.00 (n/a)	1	97.00 (n/a)
	64	1	140.00 (n/a)	1	4.00 (n/a)	1	109.00 (n/a)	1	8.00 (n/a)	1	93.00 (n/a)
	68	1	139.00 (n/a)	1	3.90 (n/a)	1	111.00 (n/a)	1	7.00 (n/a)	1	85.00 (n/a)
	72	1	141.00 (n/a)	1	3.80 (n/a)	1	107.00 (n/a)	1	6.00 (n/a)	1	90.00 (n/a)
	Death	15	138.60 (1.64)	15	6.87 (0.52)	15	110.80 (1.86)	15	26.13 (3.64)	16	85.88 (13.59)

Table A1b. Descriptive Statistics for Arterial pH, Partial Pressure of CO_2 (P_aCO_2) and of O_2 (P_aO_2), Bicarbonate Ion (HCO_3), and Total CO_2 (TCO_2) by Exposure/Treatment Groups and Study Timecourse.

Group	Study Time-course	pH		P_aCO_2 (mm Hg)		P_aO_2 (mm Hg)		HCO_3 (mmol/L)		TCO_2 (mmol/L)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/IBU	0	5	7.51 (0.01)	5	38.80 (1.89)	5	139.20 (12.26)	5	30.40 (1.12)	5	31.80 (1.16)
	1	2	7.57 (0.02)	2	35.35 (0.05)	2	124.50 (11.50)	2	32.50 (1.50)	2	33.50 (1.50)
	2	3	7.56 (0.03)	3	30.33 (0.65)	3	145.67 (2.85)	3	27.33 (2.60)	3	28.33 (2.60)
	4	5	7.57 (0.01)	5	32.44 (1.32)	5	119.80 (3.25)	5	29.80 (1.53)	5	30.80 (1.53)
	8	5	7.43 (0.04)	5	32.28 (1.08)	5	112.60 (3.46)	5	21.90 (2.14)	5	22.90 (2.14)
	12	5	7.52 (0.04)	5	27.14 (4.82)	5	114.60 (3.91)	5	21.60 (3.78)	5	22.40 (3.96)
	16	4	7.52 (0.03)	4	33.18 (1.45)	4	121.00 (9.28)	4	27.00 (1.47)	4	28.00 (1.47)
	20	4	7.51 (0.02)	4	32.40 (1.83)	4	117.75 (5.81)	4	26.00 (0.91)	4	27.00 (0.91)
	24	4	7.49 (0.04)	4	30.75 (1.31)	4	120.00 (4.22)	4	23.50 (2.02)	4	24.50 (2.02)
	28	3	7.53 (0.01)	3	29.80 (0.99)	3	113.00 (7.55)	3	25.00 (0.58)	3	26.00 (0.58)
	32	2	7.50 (0.02)	2	30.30 (0.70)	2	101.50 (8.50)	2	24.00 (2.00)	2	24.50 (1.50)
	36	3	7.52 (0.01)	3	29.87 (2.06)	3	98.00 (9.64)	3	24.33 (1.67)	3	25.33 (1.67)
	40	3	7.52 (0.02)	3	29.73 (2.37)	3	86.33 (5.90)	3	24.33 (2.67)	3	25.33 (2.67)
	44	3	7.52 (0.02)	3	33.10 (3.04)	3	98.67 (4.26)	3	26.67 (1.45)	3	27.67 (1.45)
	48	2	7.51 (0.06)	2	31.55 (1.65)	2	100.00 (29.00)	2	25.00 (2.00)	2	26.00 (2.00)
	52	2	7.50 (0.03)	2	27.60 (0.80)	2	102.00 (17.00)	2	21.50 (2.50)	2	22.50 (2.50)
	56	2	7.47 (0.03)	2	32.25 (3.25)	2	81.00 (12.00)	2	23.50 (3.50)	2	24.75 (3.75)
	60	3	7.50 (0.01)	3	32.23 (1.02)	3	86.67 (6.64)	3	25.33 (1.67)	3	26.33 (1.67)
	64	3	7.46 (0.04)	3	27.37 (1.94)	3	87.33 (13.64)	3	19.67 (2.96)	3	20.67 (2.96)
	68	3	7.49 (0.01)	3	28.27 (1.05)	2	93.50 (12.50)	3	21.67 (1.33)	3	22.67 (1.33)
	72	3	7.51 (0.02)	3	28.43 (0.24)	3	103.00 (16.44)	3	22.33 (1.20)	3	23.33 (1.20)
Air/NAC	0	2	7.47 (0.01)	2	36.20 (3.10)	2	115.00 (39.00)	2	26.00 (3.00)	2	27.50 (3.50)
	1	1	7.58 (n/a)	1	33.20 (n/a)	1	167.00 (n/a)	1	31.00 (n/a)	1	32.00 (n/a)
	2	2	7.52 (0.04)	2	29.45 (1.25)	2	149.00 (1.00)	2	24.00 (1.00)	2	25.00 (1.00)
	4	1	7.46 (n/a)	1	30.30 (n/a)	1	377.00 (n/a)	1	22.00 (n/a)	1	23.00 (n/a)
	8	2	7.53 (0.01)	2	32.20 (3.30)	2	121.50 (17.50)	2	27.00 (2.00)	2	28.00 (2.00)
	12	2	7.53 (0.01)	2	31.00 (1.90)	2	117.00 (18.00)	2	26.00 (1.00)	2	27.00 (1.00)
	16	2	7.53 (0.01)	2	31.60 (1.60)	2	117.00 (4.00)	2	27.00 (1.00)	2	27.50 (1.50)
	20	2	7.51 (0.03)	2	29.30 (0.80)	2	117.50 (9.50)	2	23.50 (2.50)	2	24.00 (2.00)
	24	2	7.52 (0.02)	2	31.65 (3.05)	2	103.50 (9.50)	2	26.00 (2.00)	2	27.00 (2.00)
	28	2	7.51 (0.04)	2	25.90 (1.40)	2	106.50 (4.50)	2	21.00 (3.00)	2	22.00 (3.00)
	32	1	7.57 (n/a)	1	30.10 (n/a)	1	93.00 (n/a)	1	27.00 (n/a)	1	28.00 (n/a)
	36	2	7.56 (0.02)	2	27.80 (1.80)	2	114.00 (6.00)	2	25.00 (3.00)	2	26.00 (3.00)
	40	2	7.56 (0.02)	2	29.35 (0.95)	2	106.00 (1.00)	2	26.50 (2.50)	2	27.00 (2.00)
	44	2	7.54 (0.04)	2	25.50 (2.10)	2	113.50 (7.50)	2	22.50 (3.50)	2	23.00 (4.00)
	48	2	7.55 (0.03)	2	22.40 (1.80)	2	117.50 (14.50)	2	19.50 (2.50)	2	20.50 (2.50)
	52	1	7.50 (n/a)	1	19.60 (n/a)	1	134.00 (n/a)	1	15.00 (n/a)	1	16.00 (n/a)
	56	1	7.49 (n/a)	1	25.60 (n/a)	1	104.50 (n/a)	1	19.50 (n/a)	1	20.50 (n/a)
	60	2	7.47 (0.04)	2	30.55 (3.65)	2	88.50 (25.50)	2	22.50 (0.50)	2	23.50 (0.50)
	64	2	7.48 (0.04)	2	28.85 (3.95)	2	78.00 (25.00)	2	21.00 (1.00)	2	22.00 (1.00)
	68	2	7.50 (0.00)	2	25.25 (5.35)	2	93.50 (30.50)	2	20.00 (4.00)	2	20.50 (4.50)
	72	2	7.52 (0.01)	2	24.50 (4.80)	2	103.00 (30.00)	2	20.00 (4.00)	2	20.50 (4.50)

Table A1b. Descriptive Statistics for Arterial pH, Partial Pressure of CO_2 (P_aCO_2) and of O_2 (P_aO_2), Bicarbonate Ion (HCO_3), and Total CO_2 (TCO_2) by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	pH		P_aCO_2 (mm Hg)		P_aO_2 (mm Hg)		HCO_3 (mmol/L)		TCO_2 (mmol/L)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/None	0	6	7.48 (0.02)	6	36.92 (1.78)	6	114.33 (14.87)	6	27.50 (1.31)	6	28.67 (1.31)
	1	5	7.53 (0.01)	5	29.82 (0.84)	5	149.80 (4.47)	5	25.00 (1.48)	5	26.00 (1.48)
	2	1	7.51 (n/a)	1	35.40 (n/a)	1	102.00 (n/a)	1	29.00 (n/a)	1	30.00 (n/a)
	4	6	7.52 (0.02)	6	32.52 (1.29)	6	123.00 (3.71)	6	26.50 (0.34)	6	27.50 (0.34)
	8	6	7.50 (0.02)	6	33.90 (1.79)	6	111.50 (5.67)	6	26.33 (1.58)	6	27.50 (1.52)
	12	6	7.50 (0.02)	6	33.57 (1.99)	6	111.33 (5.60)	6	26.17 (1.19)	6	27.33 (1.28)
	16	5	7.51 (0.02)	5	32.16 (2.33)	5	110.60 (4.63)	5	25.80 (1.56)	5	26.80 (1.77)
	20	5	7.52 (0.01)	5	28.92 (1.48)	5	121.00 (3.79)	5	23.20 (0.66)	5	24.00 (0.63)
	24	5	7.50 (0.01)	5	28.30 (2.09)	5	122.80 (5.84)	5	21.80 (1.11)	5	22.80 (1.11)
	28	5	7.50 (0.02)	5	27.54 (1.66)	5	112.60 (10.31)	5	21.40 (1.21)	5	22.20 (1.16)
	32	5	7.50 (0.02)	5	30.32 (1.95)	5	107.80 (8.42)	5	24.00 (1.10)	5	24.80 (1.07)
	36	4	7.52 (0.01)	4	29.05 (2.02)	4	102.50 (6.49)	4	23.75 (1.25)	4	24.75 (1.25)
	40	5	7.51 (0.01)	5	27.06 (1.53)	5	102.60 (7.23)	5	21.80 (1.46)	5	22.60 (1.50)
	44	6	7.51 (0.01)	6	28.62 (1.31)	6	103.67 (4.00)	6	22.83 (1.01)	6	23.83 (1.14)
	48	5	7.51 (0.02)	5	24.90 (0.97)	5	110.00 (5.07)	5	19.60 (0.60)	5	20.40 (0.75)
	52	5	7.50 (0.02)	5	25.58 (2.07)	5	97.60 (6.87)	5	19.80 (1.39)	5	20.60 (1.29)
	56	5	7.51 (0.02)	5	26.36 (1.66)	5	109.40 (5.20)	5	21.40 (1.21)	5	22.20 (1.36)
	60	5	7.50 (0.01)	5	25.94 (1.54)	5	103.00 (9.61)	5	20.00 (0.84)	5	21.00 (0.84)
	64	6	7.50 (0.01)	6	27.17 (2.22)	6	92.83 (4.47)	6	21.00 (1.57)	6	21.83 (1.70)
	68	5	7.51 (0.01)	5	23.64 (0.58)	5	108.20 (2.40)	5	18.60 (0.40)	5	19.40 (0.40)
	72	6	7.51 (0.01)	6	23.97 (1.71)	6	109.67 (4.30)	6	18.83 (1.35)	6	19.83 (1.35)
CG/IBU	0	6	7.51 (0.01)	6	34.97 (0.72)	6	135.83 (4.76)	6	27.67 (0.88)	6	28.67 (0.88)
	1	5	7.47 (0.02)	5	39.48 (2.27)	5	63.60 (3.56)	5	29.00 (1.22)	5	30.00 (1.22)
	2	1	7.53 (n/a)	1	33.00 (n/a)	1	83.00 (n/a)	1	28.00 (n/a)	1	29.00 (n/a)
	4	5	7.40 (0.03)	5	41.72 (6.68)	5	74.80 (7.86)	5	25.80 (3.54)	5	27.20 (3.68)
	8	6	7.32 (0.04)	6	52.58 (5.20)	6	54.38 (5.85)	6	26.48 (0.65)	6	28.07 (0.68)
	12	4	7.27 (0.07)	4	56.78 (7.05)	4	53.25 (9.38)	4	25.50 (1.32)	4	27.00 (1.22)
	16	3	7.38 (0.06)	3	48.90 (10.36)	3	66.00 (10.79)	3	28.00 (2.00)	3	29.33 (2.33)
	20	3	7.37 (0.05)	3	50.63 (6.59)	3	60.67 (5.90)	3	29.33 (0.67)	3	30.67 (0.88)
	24	3	7.42 (0.04)	3	45.03 (5.85)	3	68.33 (4.67)	3	28.67 (1.20)	3	29.67 (1.20)
	28	3	7.32 (0.12)	3	60.87 (16.92)	3	55.67 (12.41)	3	29.33 (1.86)	3	31.33 (2.03)
	32	2	7.42 (0.06)	2	49.60 (13.60)	2	62.00 (7.00)	2	31.50 (4.50)	2	33.00 (5.00)
	36	2	7.49 (0.06)	2	41.00 (10.40)	2	72.00 (16.00)	2	30.50 (3.50)	2	32.00 (4.00)
	40	2	7.50 (0.04)	2	40.55 (9.35)	2	67.50 (20.50)	2	30.50 (4.50)	2	32.00 (5.00)
	44	2	7.49 (0.07)	2	42.50 (17.40)	2	62.00 (22.00)	2	30.50 (8.50)	2	31.50 (8.50)
	48	2	7.50 (0.05)	2	37.90 (13.30)	2	57.50 (18.50)	2	29.00 (7.00)	2	29.50 (7.50)
	52	2	7.49 (0.07)	2	45.30 (18.10)	2	65.50 (21.50)	2	33.00 (8.00)	2	34.50 (8.50)
	56	2	7.49 (0.04)	2	42.75 (11.95)	2	64.00 (24.00)	2	31.50 (5.50)	2	33.00 (6.00)
	60	2	7.49 (0.09)	2	38.80 (13.80)	2	59.50 (28.50)	2	28.50 (4.50)	2	29.50 (5.50)
	64	2	7.51 (0.03)	2	41.90 (17.60)	2	58.00 (19.00)	2	32.50 (11.50)	2	34.00 (12.00)
	68	2	7.48 (0.08)	2	46.15 (19.35)	2	52.00 (23.00)	2	32.50 (8.50)	2	33.75 (8.75)
	72	2	7.46 (0.10)	2	44.30 (18.70)	2	57.50 (31.50)	2	29.00 (6.00)	2	30.50 (6.50)

Table A1b. Descriptive Statistics for Arterial pH, Partial Pressure of CO_2 (P_aCO_2) and of O_2 (P_aO_2), Bicarbonate Ion (HCO_3), and Total CO_2 (TCO_2) by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	pH		P_aCO_2 (mm Hg)		P_aO_2 (mm Hg)		HCO_3 (mmol/L)		TCO_2 (mmol/L)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/NAC	0	3	7.52 (0.01)	3	37.07 (0.79)	3	129.33 (5.78)	3	30.00 (1.15)	3	31.00 (1.15)
	1	3	7.44 (0.04)	3	41.53 (4.37)	3	74.00 (12.50)	3	28.00 (0.58)	3	29.00 (0.58)
	4	3	7.44 (0.05)	3	45.52 (4.73)	3	68.50 (10.98)	3	30.00 (0.58)	3	31.17 (0.44)
	8	2	7.42 (0.02)	2	37.45 (9.65)	2	59.50 (2.50)	2	24.00 (7.00)	2	25.50 (7.50)
	12	2	7.40 (0.05)	2	50.40 (7.70)	2	51.50 (10.50)	2	31.00 (1.00)	2	32.00 (1.00)
	16	1	7.51 (n/a)	1	36.10 (n/a)	1	65.00 (n/a)	1	29.00 (n/a)	1	30.00 (n/a)
	20	1	7.48 (n/a)	1	28.40 (n/a)	1	70.00 (n/a)	1	21.00 (n/a)	1	22.00 (n/a)
	24	1	7.49 (n/a)	1	31.30 (n/a)	1	78.00 (n/a)	1	24.00 (n/a)	1	25.00 (n/a)
	28	1	7.53 (n/a)	1	35.90 (n/a)	1	85.00 (n/a)	1	30.00 (n/a)	1	31.00 (n/a)
	32	1	7.48 (n/a)	1	37.40 (n/a)	1	85.00 (n/a)	1	28.00 (n/a)	1	29.00 (n/a)
	36	1	7.49 (n/a)	1	28.80 (n/a)	1	90.00 (n/a)	1	22.00 (n/a)	1	23.00 (n/a)
	40	1	7.48 (n/a)	1	29.60 (n/a)	1	86.00 (n/a)	1	22.00 (n/a)	1	23.00 (n/a)
	44	1	7.48 (n/a)	1	28.50 (n/a)	1	95.00 (n/a)	1	21.00 (n/a)	1	22.00 (n/a)
	48	1	7.54 (n/a)	1	29.00 (n/a)	1	94.00 (n/a)	1	25.00 (n/a)	1	26.00 (n/a)
	52	1	7.53 (n/a)	1	30.20 (n/a)	1	91.00 (n/a)	1	25.00 (n/a)	1	26.00 (n/a)
	56	1	7.53 (n/a)	1	27.10 (n/a)	1	96.00 (n/a)	1	23.00 (n/a)	1	24.00 (n/a)
	60	1	7.54 (n/a)	1	27.90 (n/a)	1	95.00 (n/a)	1	24.00 (n/a)	1	25.00 (n/a)
	64	1	7.51 (n/a)	1	30.70 (n/a)	1	82.00 (n/a)	1	25.00 (n/a)	1	26.00 (n/a)
	68	1	7.56 (n/a)	1	26.40 (n/a)	1	101.00 (n/a)	1	23.00 (n/a)	1	24.00 (n/a)
	72	1	7.52 (n/a)	1	23.50 (n/a)	1	88.00 (n/a)	1	19.00 (n/a)	1	20.00 (n/a)
CG/None	0	6	7.49 (0.02)	6	38.88 (1.38)	6	136.00 (8.01)	6	30.00 (1.13)	6	31.17 (1.17)
	1	5	7.47 (0.03)	5	39.62 (2.70)	5	84.00 (10.22)	5	28.60 (1.21)	5	29.60 (1.21)
	2	1	7.57 (n/a)	1	22.50 (n/a)	1	83.00 (n/a)	1	20.00 (n/a)	1	21.00 (n/a)
	4	6	7.47 (0.03)	6	40.70 (3.80)	6	88.17 (6.44)	6	29.33 (0.95)	6	30.50 (1.18)
	8	6	7.41 (0.03)	6	40.48 (5.52)	6	73.08 (7.17)	6	25.50 (2.88)	6	26.67 (3.13)
	12	5	7.44 (0.02)	5	37.86 (5.47)	5	81.53 (5.54)	5	25.00 (2.66)	5	26.23 (2.88)
	16	2	7.37 (0.05)	2	49.75 (6.95)	2	67.50 (0.50)	2	29.00 (1.00)	2	30.00 (1.00)
	20	2	7.43 (0.05)	2	50.95 (9.15)	2	67.50 (2.50)	2	33.00 (2.00)	2	35.00 (2.00)
	24	2	7.33 (0.16)	2	62.40 (24.80)	2	56.00 (22.00)	2	30.50 (1.50)	2	32.50 (2.50)
	28	1	7.49 (n/a)	1	39.40 (n/a)	1	77.00 (n/a)	1	30.00 (n/a)	1	31.00 (n/a)
	32	1	7.49 (n/a)	1	36.00 (n/a)	1	74.00 (n/a)	1	27.00 (n/a)	1	29.00 (n/a)
	36	1	7.52 (n/a)	1	36.10 (n/a)	1	91.00 (n/a)	1	29.00 (n/a)	1	30.00 (n/a)
	72	1	7.49 (n/a)	1	20.70 (n/a)	1	126.00 (n/a)	1	16.00 (n/a)	1	17.00 (n/a)

Table A1b. Descriptive Statistics for Arterial pH, Partial Pressure of CO_2 (P_aCO_2) and of O_2 (P_aO_2), Bicarbonate Ion (HCO_3), and Total CO_2 (TCO_2) by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	pH		P_aCO_2 (mm Hg)		P_aO_2 (mm Hg)		HCO_3 (mmol/L)		TCO_2 (mmol/L)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/PEEP	0	4	7.42 (0.04)	4	35.65 (2.71)	4	97.25 (11.49)	4	23.25 (2.66)	4	24.75 (2.78)
	1	4	7.47 (0.02)	4	34.73 (1.24)	4	139.00 (37.61)	4	25.50 (0.65)	4	26.50 (0.65)
	4	4	7.39 (0.03)	4	44.51 (4.41)	4	91.00 (30.72)	4	26.88 (1.85)	4	28.25 (2.03)
	8	3	7.39 (0.01)	3	40.03 (6.26)	3	133.00 (37.03)	3	24.33 (4.26)	3	25.67 (4.37)
	12	2	7.38 (0.04)	2	45.45 (1.35)	2	114.00 (18.00)	2	27.00 (3.00)	2	28.50 (3.50)
	16	2	7.56 (0.14)	2	33.50 (14.60)	2	149.00 (30.00)	2	27.50 (4.50)	2	28.50 (4.50)
	20	1	7.46 (n/a)	1	47.20 (n/a)	1	103.00 (n/a)	1	33.00 (n/a)	1	35.00 (n/a)
	24	1	7.48 (n/a)	1	37.50 (n/a)	1	144.00 (n/a)	1	28.00 (n/a)	1	29.00 (n/a)
	28	1	7.44 (n/a)	1	41.60 (n/a)	1	106.00 (n/a)	1	28.00 (n/a)	1	29.00 (n/a)
	32	1	7.45 (n/a)	1	46.00 (n/a)	1	106.00 (n/a)	1	32.00 (n/a)	1	33.00 (n/a)
	36	1	7.48 (n/a)	1	45.40 (n/a)	1	116.00 (n/a)	1	34.00 (n/a)	1	35.00 (n/a)
	40	1	7.48 (n/a)	1	34.00 (n/a)	1	143.00 (n/a)	1	25.00 (n/a)	1	26.00 (n/a)
	44	1	7.48 (n/a)	1	27.90 (n/a)	1	155.00 (n/a)	1	21.00 (n/a)	1	22.00 (n/a)
	48	1	7.52 (n/a)	1	31.30 (n/a)	1	156.00 (n/a)	1	26.00 (n/a)	1	26.00 (n/a)
	52	1	7.56 (n/a)	1	30.40 (n/a)	1	162.00 (n/a)	1	27.00 (n/a)	1	28.00 (n/a)
	56	1	7.42 (n/a)	1	42.50 (n/a)	1	90.00 (n/a)	1	28.00 (n/a)	1	29.00 (n/a)
	60	1	7.42 (n/a)	1	43.80 (n/a)	1	110.00 (n/a)	1	28.00 (n/a)	1	30.00 (n/a)
	64	1	7.46 (n/a)	1	35.70 (n/a)	1	80.00 (n/a)	1	25.00 (n/a)	1	26.00 (n/a)
	68	1	7.46 (n/a)	1	35.90 (n/a)	1	106.00 (n/a)	1	25.00 (n/a)	1	26.00 (n/a)
	72	1	7.29 (n/a)	1	60.40 (n/a)	1	65.00 (n/a)	1	29.00 (n/a)	1	31.00 (n/a)
	Death	14	7.35 (0.05)	14	47.29 (7.20)	15	61.53 (11.77)	14	22.43 (1.91)	14	23.79 (2.07)

Table A1c. Descriptive Statistics for Oxygen Saturation, Base Excess, Anion Gap, Hemoglobin, and Hematocrit by Exposure/Treatment Groups and Study Timecourse.

Group	Study Time-course	Oxygen Saturation (%)		Base Excess (mmol/L)		Anion Gap (mmol/L)		Hemoglobin (g/dL)		Hematocrit (%)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/IBU	0	5	99.60 (0.24)	5	7.60 (1.17)	5	9.20 (0.58)	5	8.00 (0.32)	5	23.00 (0.84)
	1	2	99.00 (0.00)	2	10.00 (2.00)	2	11.00 (1.00)	2	8.50 (0.50)	2	24.50 (0.50)
	2	3	99.67 (0.33)	3	5.00 (3.21)	3	9.67 (1.20)	3	7.00 (0.58)	3	20.67 (1.45)
	4	5	99.00 (0.00)	5	8.00 (1.58)	5	9.60 (0.51)	5	7.60 (0.40)	5	23.20 (1.07)
	8	5	98.60 (0.29)	5	-2.50 (2.63)	5	14.60 (2.64)	5	7.33 (0.74)	5	21.73 (2.12)
	12	5	98.80 (0.20)	5	-1.40 (3.70)	5	14.60 (3.31)	5	6.40 (0.40)	5	19.00 (0.89)
	16	4	99.00 (0.41)	4	4.00 (1.78)	3	9.00 (0.00)	4	6.58 (0.42)	4	19.92 (1.49)
	20	4	98.75 (0.25)	4	3.00 (1.08)	4	9.75 (1.55)	4	7.25 (0.25)	4	20.75 (0.75)
	24	4	98.75 (0.25)	4	0.25 (2.56)	4	10.75 (1.89)	4	6.00 (0.00)	4	18.00 (0.41)
	28	3	98.67 (0.33)	3	2.33 (0.88)	3	8.33 (1.33)	3	6.67 (0.88)	3	20.67 (2.40)
	32	2	98.50 (0.50)	2	0.50 (2.50)	2	11.50 (4.50)	2	7.00 (1.00)	2	20.50 (2.50)
	36	3	98.33 (0.67)	3	1.33 (1.76)	3	12.33 (0.88)	3	5.33 (0.88)	3	15.67 (2.91)
	40	3	97.33 (0.33)	3	1.67 (2.85)	3	12.33 (0.33)	3	9.33 (0.88)	3	27.00 (2.31)
	44	3	98.33 (0.33)	3	3.67 (1.45)	3	10.00 (1.00)	3	10.00 (1.15)	3	29.00 (3.79)
	48	2	97.00 (2.00)	2	2.00 (3.00)	2	8.00 (1.00)	2	9.50 (1.50)	2	27.50 (4.50)
	52	2	98.00 (1.00)	2	-2.00 (3.00)	2	12.50 (2.50)	2	13.00 (4.00)	2	37.00 (12.00)
	56	2	96.25 (1.25)	2	0.00 (4.00)	2	10.00 (0.00)	2	8.75 (1.25)	2	25.00 (3.00)
	60	3	97.33 (0.67)	3	2.33 (1.67)	3	10.00 (1.15)	3	9.67 (0.88)	3	28.00 (2.31)
	64	3	96.67 (1.45)	3	-3.67 (3.28)	2	10.50 (1.50)	3	11.33 (2.19)	3	33.33 (6.77)
	68	2	98.00 (1.00)	3	-2.00 (1.53)	3	13.33 (4.33)	3	8.33 (0.88)	3	25.33 (2.40)
	72	3	97.67 (0.88)	3	-0.67 (1.76)	3	9.67 (2.03)	3	7.67 (0.67)	3	23.33 (1.86)
Air/NAC	0	2	97.50 (1.50)	2	2.50 (3.50)	2	6.00 (1.00)	2	7.50 (0.50)	2	22.50 (0.50)
	1	1	100.00 (n/a)	1	10.00 (n/a)	1	10.00 (n/a)	1	9.00 (n/a)	1	26.00 (n/a)
	2	2	99.50 (0.50)	2	1.50 (1.50)	2	8.50 (1.50)	2	6.50 (0.50)	2	20.00 (1.00)
	4	1	100.00 (n/a)	1	-2.00 (n/a)	1	5.00 (n/a)	1	7.00 (n/a)	1	22.00 (n/a)
	8	2	99.00 (0.00)	2	4.50 (2.50)	2	10.50 (0.50)	2	9.00 (1.00)	2	26.50 (2.50)
	12	2	98.50 (0.50)	2	3.00 (1.00)	2	10.00 (1.00)	1	8.00 (n/a)	2	27.50 (4.50)
	16	2	99.00 (0.00)	2	4.00 (1.00)	2	8.50 (2.50)	2	8.50 (1.50)	2	25.00 (5.00)
	20	2	99.00 (0.00)	2	0.50 (2.50)	2	11.00 (1.00)	2	8.50 (1.50)	2	24.50 (4.50)
	24	2	98.50 (0.50)	2	3.00 (1.00)	2	9.50 (2.50)	2	9.00 (2.00)	2	26.50 (5.50)
	28	2	99.00 (0.00)	2	-2.00 (4.00)	2	5.50 (2.50)	2	7.00 (0.00)	2	21.50 (0.50)
	32	1	98.00 (n/a)	1	5.00 (n/a)	1	8.00 (n/a)	1	8.00 (n/a)	1	24.00 (n/a)
	36	2	99.00 (0.00)	2	3.00 (3.00)	1	13.00 (n/a)	2	10.00 (3.00)	2	30.00 (8.00)
	40	2	99.00 (0.00)	2	4.00 (3.00)	2	9.50 (3.50)	2	10.00 (1.00)	2	28.50 (3.50)
	44	2	99.00 (0.00)	2	0.00 (4.00)	2	7.50 (0.50)	2	6.50 (0.50)	2	20.00 (1.00)
	48	2	99.00 (0.00)	2	-3.00 (3.00)	2	7.50 (0.50)	2	6.50 (0.50)	2	19.50 (1.50)
	52	1	99.00 (n/a)	1	-8.00 (n/a)	1	6.00 (n/a)	1	7.00 (n/a)	1	20.00 (n/a)
	56	1	99.00 (n/a)	1	-4.00 (n/a)	1	11.00 (n/a)	1	9.50 (n/a)	1	27.00 (n/a)
	60	2	96.00 (3.00)	2	-1.50 (0.50)	2	11.00 (2.00)	2	13.00 (2.00)	2	38.00 (5.00)
	64	2	93.50 (5.50)	2	-2.50 (0.50)	2	11.00 (6.00)	2	13.50 (4.50)	2	38.50 (13.50)
	68	2	96.50 (2.50)	2	-3.00 (4.00)	2	7.50 (1.50)	2	7.50 (0.50)	2	22.50 (0.50)
	72	2	97.50 (1.50)	2	-2.50 (4.50)	2	6.50 (3.50)	2	7.50 (0.50)	2	22.00 (1.00)

Table A1c. Descriptive Statistics for Oxygen Saturation, Base Excess, Anion Gap, Hemoglobin, and Hematocrit by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Oxygen Saturation (%)		Base Excess (mmol/L)		Anion Gap (mmol/L)		Hemoglobin (g/dL)		Hematocrit (%)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/None	0	6	97.83 (0.91)	6	4.00 (1.46)	6	8.50 (1.12)	6	8.00 (0.45)	6	23.33 (1.15)
	1	5	99.80 (0.20)	5	2.60 (1.69)	5	7.60 (0.81)	5	6.80 (0.66)	5	20.40 (1.50)
	2	1	98.00 (n/a)	1	6.00 (n/a)	1	8.00 (n/a)	1	8.00 (n/a)	1	23.00 (n/a)
	4	6	99.00 (0.00)	6	3.67 (0.42)	6	8.67 (0.84)	6	7.33 (0.56)	6	22.17 (1.45)
	8	6	98.33 (0.21)	6	3.17 (1.66)	6	10.00 (0.63)	6	8.50 (0.76)	6	25.50 (2.05)
	12	6	98.67 (0.21)	6	3.17 (1.33)	6	10.83 (0.60)	6	9.17 (1.08)	6	27.00 (3.21)
	16	5	98.80 (0.20)	5	3.00 (1.67)	6	8.67 (1.15)	6	8.00 (0.52)	6	23.33 (1.48)
	20	5	99.00 (0.00)	5	0.60 (0.51)	5	7.80 (1.24)	5	7.40 (0.75)	5	21.60 (2.01)
	24	5	98.80 (0.20)	5	-0.80 (0.92)	5	7.40 (1.03)	5	7.20 (0.80)	5	20.80 (2.08)
	28	5	98.40 (0.40)	5	-1.60 (1.17)	4	8.50 (1.19)	5	6.60 (0.24)	5	19.60 (0.51)
	32	5	98.40 (0.40)	5	0.60 (0.93)	5	10.60 (0.51)	5	8.60 (0.51)	5	24.80 (1.56)
	36	4	98.25 (0.48)	4	1.00 (1.22)	4	12.00 (0.71)	4	11.75 (1.93)	4	34.00 (5.35)
	40	5	98.40 (0.40)	5	-1.40 (1.50)	5	11.80 (1.32)	5	8.80 (0.86)	5	25.20 (2.35)
	44	6	98.83 (0.17)	6	0.00 (1.06)	6	9.33 (1.09)	6	8.17 (0.48)	6	23.50 (1.41)
	48	5	98.80 (0.20)	5	-3.40 (0.81)	5	11.20 (2.35)	5	8.00 (1.14)	5	23.20 (3.40)
	52	5	98.00 (0.55)	5	-3.00 (1.41)	5	10.40 (1.54)	5	7.20 (0.80)	5	21.00 (2.19)
	56	5	98.80 (0.20)	5	-2.00 (1.38)	5	11.80 (0.97)	5	9.20 (0.80)	5	26.40 (2.44)
	60	5	98.20 (0.37)	5	-2.60 (0.93)	5	12.00 (0.71)	5	8.40 (0.68)	5	24.20 (2.08)
	64	6	98.00 (0.26)	6	-1.83 (1.60)	6	9.50 (1.84)	6	8.00 (0.82)	6	23.67 (2.42)
	68	5	98.80 (0.20)	5	-4.40 (0.68)	5	11.80 (1.20)	5	7.80 (0.80)	5	22.60 (2.25)
	72	6	98.83 (0.17)	6	-4.17 (1.45)	6	9.67 (0.76)	6	6.50 (0.34)	6	19.83 (0.98)
CG/IBU	0	6	99.00 (0.00)	6	4.50 (0.99)	6	10.83 (0.98)	6	8.00 (0.37)	6	23.67 (1.15)
	1	5	92.80 (0.86)	5	5.20 (1.16)	4	9.75 (1.03)	5	7.80 (0.37)	5	22.80 (0.86)
	2	1	97.00 (n/a)	1	5.00 (n/a)	1	11.00 (n/a)	1	7.00 (n/a)	1	22.00 (n/a)
	4	5	92.20 (3.85)	5	1.20 (3.51)	5	11.20 (1.46)	5	8.60 (0.93)	5	24.80 (2.31)
	8	6	76.47 (5.94)	6	0.20 (0.78)	6	13.10 (1.38)	6	9.60 (0.75)	6	27.89 (2.11)
	12	4	73.25 (12.00)	4	-1.25 (2.36)	4	10.50 (1.66)	4	9.00 (0.82)	4	26.50 (2.66)
	16	3	88.00 (7.55)	3	2.67 (1.20)	2	7.50 (1.50)	3	8.33 (1.33)	3	25.00 (3.00)
	20	3	88.00 (5.51)	3	3.67 (0.67)	3	9.33 (0.33)	3	8.67 (0.67)	3	26.00 (2.00)
	24	3	93.00 (1.73)	3	4.00 (0.58)	3	9.00 (1.00)	3	8.33 (0.88)	3	24.67 (2.19)
	28	3	75.33 (16.83)	3	3.00 (2.89)	3	8.67 (0.88)	3	9.33 (0.67)	3	27.33 (2.19)
	32	2	90.50 (4.50)	2	6.50 (3.50)	2	10.00 (1.00)	2	10.50 (0.50)	2	31.00 (1.00)
	36	2	93.50 (4.50)	2	7.00 (3.00)	2	10.00 (1.00)	2	9.50 (0.50)	2	27.00 (1.00)
	40	2	91.00 (7.00)	2	7.50 (3.50)	2	8.00 (0.00)	2	9.50 (0.50)	2	27.00 (2.00)
	44	2	86.00 (12.00)	2	7.00 (7.00)	2	3.50 (1.50)	2	8.50 (1.50)	2	25.50 (4.50)
	48	2	86.00 (11.00)	2	5.50 (6.50)	2	4.00 (1.00)	2	8.00 (1.00)	2	23.00 (3.00)
	52	2	88.00 (10.00)	2	10.00 (7.00)	2	8.00 (1.00)	2	10.00 (1.00)	2	29.00 (3.00)
	56	2	87.00 (11.00)	2	8.00 (5.00)	2	6.00 (2.00)	2	9.50 (1.50)	2	27.00 (4.00)
	60	2	78.00 (20.00)	2	5.50 (3.50)	2	5.50 (0.50)	2	11.50 (1.50)	2	33.00 (4.00)
	64	2	86.00 (11.00)	2	9.50 (11.50)	2	4.00 (1.00)	2	11.00 (2.00)	2	32.00 (7.00)
	68	2	74.75 (22.25)	2	8.75 (7.75)	2	4.75 (0.25)	2	11.25 (1.75)	2	32.50 (4.50)
	72	2	70.50 (27.50)	2	5.00 (4.00)	2	6.00 (1.00)	2	8.50 (0.50)	2	25.00 (2.00)

Table A1c. Descriptive Statistics for Oxygen Saturation, Base Excess, Anion Gap, Hemoglobin, and Hematocrit by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Oxygen Saturation (%)		Base Excess (mmol/L)		Anion Gap (mmol/L)		Hemoglobin (g/dL)		Hematocrit (%)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/NAC	0	3	99.00 (0.00)	3	7.00 (1.15)	3	7.33 (0.67)	3	8.67 (0.33)	3	25.33 (0.67)
	1	3	93.33 (2.40)	3	4.00 (0.58)	3	9.67 (0.67)	3	8.67 (0.33)	3	25.00 (0.58)
	4	3	85.33 (12.17)	3	5.83 (1.30)	2	8.25 (0.75)	3	8.33 (1.74)	3	24.17 (5.34)
	8	2	91.00 (1.00)	2	0.00 (7.00)	2	12.50 (2.50)	2	10.50 (1.50)	2	30.50 (3.50)
	12	2	81.50 (10.50)	2	6.00 (0.00)	2	10.00 (3.00)	2	13.50 (1.50)	2	40.00 (4.00)
	16	1	94.00 (n/a)	1	6.00 (n/a)	1	12.00 (n/a)	1	10.00 (n/a)	1	28.00 (n/a)
	20	1	95.00 (n/a)	1	-2.00 (n/a)	1	8.00 (n/a)	1	7.00 (n/a)	1	21.00 (n/a)
	24	1	97.00 (n/a)	1	1.00 (n/a)	1	7.00 (n/a)	1	7.00 (n/a)	1	21.00 (n/a)
	28	1	98.00 (n/a)	1	7.00 (n/a)	1	10.00 (n/a)	1	9.00 (n/a)	1	27.00 (n/a)
	32	1	97.00 (n/a)	1	4.00 (n/a)	1	10.00 (n/a)	1	9.00 (n/a)	1	26.00 (n/a)
	36	1	98.00 (n/a)	1	-1.00 (n/a)	1	7.00 (n/a)	1	7.00 (n/a)	1	20.00 (n/a)
	40	1	97.00 (n/a)	1	-2.00 (n/a)	1	9.00 (n/a)	1	7.00 (n/a)	1	22.00 (n/a)
	44	1	98.00 (n/a)	1	-2.00 (n/a)	1	8.00 (n/a)	1	6.00 (n/a)	1	19.00 (n/a)
	48	1	98.00 (n/a)	1	2.00 (n/a)	1	12.00 (n/a)	1	8.00 (n/a)	1	24.00 (n/a)
	52	1	98.00 (n/a)	1	2.00 (n/a)	1	13.00 (n/a)	1	10.00 (n/a)	1	30.00 (n/a)
	56	1	98.00 (n/a)	1	0.00 (n/a)	1	13.00 (n/a)	1	8.00 (n/a)	1	24.00 (n/a)
	60	1	98.00 (n/a)	1	1.00 (n/a)	1	14.00 (n/a)	1	9.00 (n/a)	1	27.00 (n/a)
	64	1	97.00 (n/a)	1	2.00 (n/a)	1	13.00 (n/a)	1	9.00 (n/a)	1	25.00 (n/a)
	68	1	99.00 (n/a)	1	1.00 (n/a)	1	15.00 (n/a)	1	9.00 (n/a)	1	27.00 (n/a)
	72	1	98.00 (n/a)	1	-4.00 (n/a)	1	12.00 (n/a)	1	7.00 (n/a)	1	20.00 (n/a)
CG/None	0	6	99.33 (0.21)	6	6.83 (1.49)	6	9.00 (1.06)	6	8.50 (0.67)	6	24.67 (1.73)
	1	5	95.40 (1.50)	5	4.60 (1.25)	5	7.60 (1.03)	5	7.40 (0.81)	5	21.40 (2.29)
	2	1	98.00 (n/a)	1	-2.00 (n/a)	1	6.00 (n/a)	1	7.00 (n/a)	1	20.00 (n/a)
	4	6	96.83 (0.95)	6	5.83 (0.70)	6	9.33 (1.09)	6	9.17 (0.40)	6	26.83 (1.30)
	8	6	92.17 (3.17)	6	0.58 (2.95)	5	10.30 (1.56)	6	9.17 (0.31)	6	26.25 (0.96)
	12	5	95.37 (1.13)	5	0.97 (2.47)	5	9.60 (2.09)	5	8.90 (1.21)	5	26.17 (3.21)
	16	2	92.00 (1.00)	2	3.00 (0.00)	3	7.67 (1.33)	3	10.33 (1.76)	3	30.33 (4.81)
	20	2	93.00 (2.00)	2	9.00 (1.00)	2	8.50 (2.50)	2	10.00 (0.00)	2	30.00 (0.00)
	24	2	72.00 (24.00)	2	4.50 (0.50)	2	8.00 (2.00)	2	10.50 (1.50)	2	30.50 (3.50)
	28	1	96.00 (n/a)	1	7.00 (n/a)	1	10.00 (n/a)	1	10.00 (n/a)	1	30.00 (n/a)
	32	1	96.00 (n/a)	1	4.00 (n/a)	1	8.00 (n/a)	1	11.00 (n/a)	1	31.00 (n/a)
	36	1	98.00 (n/a)	1	6.00 (n/a)	1	11.00 (n/a)	1	11.00 (n/a)	1	33.00 (n/a)
	72	1	99.00 (n/a)	1	-7.00 (n/a)	1	10.00 (n/a)	1	7.00 (n/a)	1	21.00 (n/a)

Table A1c. Descriptive Statistics for Oxygen Saturation, Base Excess, Anion Gap, Hemoglobin, and Hematocrit by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Oxygen Saturation (%)		Base Excess (mmol/L)		Anion Gap (mmol/L)		Hemoglobin (g/dL)		Hematocrit (%)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/PEEP	0	4	97.00 (0.82)	4	-8.50 (8.74)	4	17.00 (9.35)	4	8.00 (1.41)	4	23.75 (4.27)
	1	4	98.00 (1.08)	4	1.50 (0.87)	3	7.67 (0.88)	3	7.33 (0.88)	3	22.33 (2.40)
	4	4	77.75 (20.10)	4	1.88 (2.16)	4	10.25 (1.11)	4	9.13 (0.52)	4	26.00 (1.67)
	8	3	96.67 (2.85)	3	-0.67 (4.26)	3	12.33 (2.85)	3	9.33 (1.76)	3	27.33 (4.41)
	12	2	98.50 (0.50)	2	2.00 (4.00)	2	9.50 (2.50)	2	8.50 (0.50)	2	25.50 (1.50)
	16	2	99.50 (0.50)	2	5.00 (2.00)	1	7.00 (n/a)	1	9.00 (n/a)	1	25.00 (n/a)
	20	1	98.00 (n/a)	1	9.00 (n/a)	1	6.00 (n/a)	1	7.00 (n/a)	1	21.00 (n/a)
	24	1	99.00 (n/a)	1	4.00 (n/a)	1	0.00 (n/a)	1	4.00 (n/a)	1	13.00 (n/a)
	28	1	98.00 (n/a)	1	4.00 (n/a)	1	1.00 (n/a)	1	7.00 (n/a)	1	20.00 (n/a)
	32	1	98.00 (n/a)	1	8.00 (n/a)	1	5.00 (n/a)	1	9.00 (n/a)	1	25.00 (n/a)
	36	1	99.00 (n/a)	1	10.00 (n/a)	1	6.00 (n/a)	1	7.00 (n/a)	1	20.00 (n/a)
	40	1	100.00 (n/a)	1	2.00 (n/a)	1	3.00 (n/a)	1	5.00 (n/a)	1	15.00 (n/a)
	44	1	100.00 (n/a)	1	-3.00 (n/a)	1	3.00 (n/a)	1	5.00 (n/a)	1	15.00 (n/a)
	48	1	100.00 (n/a)	1	3.00 (n/a)	1	4.00 (n/a)	1	3.00 (n/a)	1	10.00 (n/a)
	52	1	100.00 (n/a)	1	5.00 (n/a)	1	7.00 (n/a)	1	5.00 (n/a)	1	16.00 (n/a)
	56	1	97.00 (n/a)	1	3.00 (n/a)	1	10.00 (n/a)	1	7.00 (n/a)	1	22.00 (n/a)
	60	1	98.00 (n/a)	1	4.00 (n/a)	1	14.00 (n/a)	1	13.00 (n/a)	1	39.00 (n/a)
	64	1	96.00 (n/a)	1	1.00 (n/a)	1	13.00 (n/a)	1	4.00 (n/a)	1	12.00 (n/a)
	68	1	98.00 (n/a)	1	2.00 (n/a)	1	8.00 (n/a)	1	8.00 (n/a)	1	24.00 (n/a)
	72	1	89.00 (n/a)	1	2.00 (n/a)	1	9.00 (n/a)	1	9.00 (n/a)	1	26.00 (n/a)
	Death	14	68.64 (7.78)	14	-3.21 (1.61)	13	13.85 (1.58)	15	8.13 (0.80)	15	23.73 (2.33)

Table A2a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Pulse Rate by Exposure/Treatment Groups and Study Timecourse.

Group	Study Time-course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/IBU	0	5	31.60 (1.03)	5	28.20 (1.32)	5	100.00 (0.00)	3	103.33 (2.96)	5	103.40 (7.05)
	1	5	32.60 (0.68)	5	30.00 (0.63)	5	100.00 (0.00)	3	103.00 (3.46)	5	100.40 (5.39)
	2	5	32.40 (1.03)	5	30.20 (0.58)	5	100.00 (0.00)	3	110.67 (4.91)	5	105.80 (6.66)
	3	5	33.20 (1.24)	5	30.20 (0.58)	5	99.80 (0.20)	3	107.00 (11.14)	5	106.40 (6.05)
	4	5	32.20 (1.02)	5	30.20 (0.58)	5	99.60 (0.40)	3	102.33 (6.96)	5	97.20 (5.83)
	5	5	32.20 (2.13)	5	30.40 (0.51)	5	98.60 (0.87)	2	95.50 (16.50)	5	86.60 (11.31)
	6	5	33.60 (2.62)	5	29.80 (0.58)	5	96.60 (1.63)	2	92.00 (25.00)	5	87.80 (11.50)
	7	5	33.40 (3.14)	5	29.80 (0.49)	5	92.60 (3.54)	3	99.33 (27.72)	5	109.20 (18.06)
	8	5	34.00 (1.14)	5	29.80 (0.58)	5	97.80 (1.74)	2	129.50 (1.50)	4	113.50 (10.20)
	9	5	30.80 (3.22)	5	29.60 (0.68)	5	97.20 (2.13)	2	93.00 (24.00)	5	97.40 (6.79)
	10	4	35.00 (0.41)	4	29.00 (0.41)	4	98.75 (0.63)	2	103.50 (8.50)	4	105.25 (8.63)
	11	4	34.00 (0.41)	4	28.75 (0.48)	4	96.00 (2.42)	2	102.50 (8.50)	4	102.75 (3.20)
	12	4	34.25 (0.95)	4	29.00 (0.41)	4	98.75 (0.48)	1	104.00 (n/a)	4	95.25 (4.55)
	13	4	32.50 (0.96)	4	29.00 (0.71)	4	99.00 (0.41)	2	91.00 (8.00)	4	91.25 (3.94)
	14	4	32.75 (0.95)	4	29.25 (0.48)	4	98.75 (0.63)	2	92.50 (11.50)	4	96.00 (5.76)
	15	4	32.50 (1.19)	4	29.00 (0.58)	4	98.25 (0.48)	3	93.00 (7.23)	4	94.50 (4.91)
	16	4	33.25 (1.18)	4	29.25 (0.25)	4	98.50 (0.96)	3	93.00 (6.11)	4	94.25 (4.21)
	17	4	34.00 (0.82)	4	29.00 (0.00)	4	97.00 (1.78)	2	95.00 (6.00)	4	97.00 (10.35)
	18	4	34.00 (0.71)	4	28.75 (0.25)	4	97.00 (1.68)	2	98.50 (3.50)	4	96.25 (1.97)
	19	4	33.75 (1.38)	4	28.50 (0.29)	4	97.50 (0.96)	2	105.00 (4.00)	4	95.00 (5.40)
	20	4	34.00 (3.94)	4	28.75 (0.25)	4	96.25 (1.93)	2	89.00 (13.00)	4	94.75 (10.13)
	21	4	33.75 (2.50)	4	28.50 (0.29)	4	97.75 (0.48)	2	88.50 (10.50)	4	89.75 (5.39)
	22	4	32.75 (1.49)	4	28.75 (0.25)	4	96.50 (2.02)	2	91.00 (6.00)	4	88.75 (2.95)
	23	4	31.50 (1.04)	4	28.25 (0.48)	4	97.25 (1.89)	2	88.00 (5.00)	4	88.00 (2.55)
	24	4	31.25 (0.48)	4	28.25 (0.48)	4	96.75 (1.97)	2	89.50 (8.50)	4	77.25 (10.50)
	25	4	32.25 (0.85)	4	28.75 (0.25)	4	95.75 (1.75)	2	79.50 (1.50)	4	81.75 (7.31)
	26	4	32.00 (0.71)	4	28.00 (0.41)	4	97.75 (0.85)	1	80.00 (n/a)	4	85.75 (7.69)
	27	3	31.67 (0.88)	3	28.33 (0.33)	3	95.67 (1.20)	2	89.00 (6.00)	3	94.00 (6.08)
	28	3	32.67 (0.88)	3	28.67 (0.33)	3	92.67 (2.91)	2	92.50 (8.50)	3	93.67 (4.48)
	29	3	32.33 (1.20)	3	28.67 (0.33)	3	92.00 (3.00)	2	78.00 (5.00)	3	91.33 (5.49)
	30	3	32.33 (0.88)	3	28.67 (0.33)	3	93.67 (2.33)	2	85.50 (2.50)	3	97.33 (9.77)
	31	3	32.67 (1.45)	3	28.67 (0.33)	3	93.33 (0.33)	2	90.00 (5.00)	3	104.00 (13.75)
	32	3	32.00 (1.00)	3	28.67 (0.33)	3	93.33 (1.20)	2	83.50 (6.50)	3	100.00 (14.74)
	33	3	31.33 (2.03)	3	28.33 (0.33)	3	94.67 (2.60)	2	87.50 (7.50)	3	98.67 (5.93)
	34	3	31.67 (1.20)	3	29.00 (0.00)	3	98.33 (0.33)	2	85.50 (0.50)	3	90.00 (2.08)
	35	3	31.67 (1.33)	3	29.00 (0.00)	3	90.67 (0.67)	2	89.00 (5.00)	3	93.00 (0.58)
	36	3	33.67 (1.20)	3	29.00 (0.00)	3	94.67 (3.84)	2	100.50 (17.50)	3	108.67 (26.17)
	37	3	33.33 (0.67)	3	29.00 (0.00)	3	95.33 (2.73)	2	102.50 (8.50)	3	96.67 (7.88)
	38	3	31.00 (0.00)	3	29.00 (0.00)	3	95.33 (2.67)	2	86.00 (0.00)	3	83.67 (2.85)
	39	3	31.33 (0.33)	3	29.00 (0.00)	3	95.33 (1.86)	1	92.00 (n/a)	3	89.33 (5.17)
	40	3	33.00 (1.00)	3	29.00 (0.00)	3	86.00 (1.15)	1	94.00 (n/a)	3	93.00 (1.53)
	41	3	32.00 (1.15)	3	28.33 (0.33)	3	97.33 (0.67)	2	84.00 (1.00)	3	86.33 (6.98)

Table A2a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Pulse Rate by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/IBU (Cont'd)	42	3	31.67 (1.45)	3	29.00 (0.00)	3	94.00 (3.51)	2	90.50 (16.50)	3	86.67 (10.27)
	43	3	32.33 (0.88)	3	28.33 (0.67)	3	94.00 (2.31)	2	89.00 (2.00)	3	105.00 (20.30)
	44	3	31.67 (0.33)	3	28.33 (0.67)	3	98.33 (0.88)	2	92.00 (13.00)	3	88.33 (9.84)
	45	3	31.00 (1.00)	3	28.33 (0.67)	3	96.00 (3.51)	2	87.00 (14.00)	3	83.67 (9.68)
	46	3	30.00 (0.58)	3	28.67 (0.33)	3	96.67 (2.85)	2	76.50 (4.50)	3	76.67 (2.91)
	47	3	30.33 (1.20)	3	28.33 (0.33)	3	96.33 (2.73)	2	81.50 (9.50)	3	86.67 (11.89)
	48	3	30.33 (1.45)	3	29.00 (0.00)	3	98.67 (0.33)	2	93.00 (26.00)	3	87.67 (15.93)
	49	3	32.00 (2.31)	3	28.67 (0.33)	3	97.67 (1.45)	1	73.00 (n/a)	3	89.67 (12.88)
	50	3	32.00 (2.00)	3	28.67 (0.67)	3	97.33 (1.76)	2	81.50 (6.50)	3	86.67 (6.17)
	51	3	33.33 (1.76)	3	29.00 (0.58)	3	93.67 (2.91)	2	93.00 (17.00)	3	94.33 (9.53)
	52	3	33.67 (0.33)	3	29.00 (0.00)	3	94.67 (3.33)	2	104.00 (21.00)	3	101.67 (12.73)
	53	3	33.33 (0.88)	3	29.33 (0.33)	3	95.67 (1.45)	2	102.50 (22.50)	3	95.00 (13.01)
	54	3	32.67 (1.76)	3	28.67 (0.33)	3	96.33 (2.19)	2	94.50 (9.50)	3	96.67 (13.72)
	55	3	32.67 (1.86)	3	29.00 (0.00)	3	96.00 (1.53)	2	104.50 (8.50)	3	95.67 (10.11)
	56	3	33.00 (1.53)	3	29.00 (0.00)	3	98.00 (1.15)	2	105.50 (17.50)	3	94.33 (14.68)
	57	3	32.00 (1.53)	3	29.00 (0.00)	3	98.00 (1.53)	2	101.00 (21.00)	3	90.33 (15.06)
	58	3	32.00 (1.00)	3	29.00 (0.00)	3	98.00 (1.15)	1	84.00 (n/a)	3	88.00 (11.15)
	59	3	30.67 (0.88)	3	29.00 (0.00)	3	96.67 (1.67)	2	95.00 (7.00)	3	87.67 (8.69)
	60	3	32.67 (0.33)	3	28.33 (0.67)	3	95.33 (2.67)	1	83.00 (n/a)	3	86.67 (8.57)
	61	3	33.00 (0.00)	3	28.33 (0.33)	3	95.00 (1.73)	1	81.00 (n/a)	3	92.67 (13.20)
	62	3	32.33 (0.33)	3	29.00 (0.00)	3	96.67 (0.88)	1	84.00 (n/a)	3	90.67 (9.82)
	63	3	32.33 (0.33)	3	28.67 (0.33)	3	95.00 (2.08)	2	95.00 (15.00)	3	90.67 (9.68)
	64	3	32.33 (0.33)	3	28.67 (0.33)	3	97.33 (0.88)	2	107.50 (13.50)	3	98.67 (11.22)
	65	3	31.33 (0.88)	3	28.67 (0.33)	3	96.00 (1.73)	2	92.00 (20.00)	3	89.00 (14.11)
	66	3	31.00 (0.58)	3	29.00 (0.00)	3	94.67 (0.33)	2	81.00 (9.00)	3	88.00 (11.14)
	67	3	30.33 (0.33)	3	28.67 (0.33)	3	93.67 (1.45)	2	97.00 (22.00)	3	91.67 (12.88)
	68	3	30.00 (0.58)	3	28.67 (0.33)	3	97.33 (0.67)	2	91.00 (19.00)	3	87.67 (11.26)
	69	3	30.67 (0.33)	3	28.67 (0.33)	3	95.67 (1.20)	2	93.50 (19.50)	3	89.00 (12.12)
	70	3	31.33 (0.88)	3	29.00 (0.00)	3	93.33 (1.20)	2	97.50 (22.50)	3	101.33 (13.54)
	71	3	29.33 (0.88)	3	29.00 (0.00)	3	98.33 (0.67)	2	95.00 (22.00)	3	89.33 (13.91)
Air/NAC	0	2	33.50 (2.50)	2	31.50 (0.50)	2	98.00 (1.00)	1	107.00 (n/a)	2	104.00 (4.00)
	1	2	32.00 (4.00)	2	31.50 (0.50)	2	98.50 (0.50)	1	87.00 (n/a)	2	93.50 (6.50)
	2	2	34.50 (3.50)	2	27.50 (4.50)	2	100.00 (0.00)	1	91.00 (n/a)	2	97.00 (6.00)
	3	2	34.50 (1.50)	2	24.50 (7.50)	2	99.00 (1.00)	1	95.00 (n/a)	2	103.00 (8.00)
	4	2	35.50 (2.50)	2	24.50 (7.50)	2	99.75 (0.25)	1	106.00 (n/a)	2	98.75 (4.75)
	5	2	35.50 (3.50)	2	27.50 (4.50)	2	96.50 (0.50)	2	104.00 (12.00)	2	104.00 (11.00)
	6	2	35.50 (1.50)	2	28.50 (2.50)	2	99.50 (0.50)	2	100.00 (12.00)	2	100.50 (12.50)
	7	2	34.50 (1.50)	2	29.50 (1.50)	2	99.50 (0.50)	2	108.00 (2.00)	2	108.00 (2.00)
	8	2	33.00 (2.00)	2	30.50 (1.50)	2	100.00 (0.00)	2	93.50 (13.50)	2	95.00 (12.00)
	9	2	33.50 (0.50)	2	29.50 (1.50)	2	99.00 (1.00)	2	137.00 (39.00)	2	93.00 (6.00)
	10	2	33.00 (1.00)	2	29.50 (1.50)	2	98.50 (0.50)	2	92.50 (1.50)	2	91.50 (2.50)
	11	2	32.50 (0.50)	2	30.00 (2.00)	2	98.50 (0.50)	2	91.00 (8.00)	2	91.50 (8.50)

Table A2a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Pulse Rate by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/NAC (Cont'd)	12	2	33.00 (2.00)	2	29.50 (2.50)	2	98.50 (1.50)	2	95.00 (17.00)	2	96.00 (17.00)
	13	2	32.50 (1.50)	2	29.50 (2.50)	2	98.50 (1.50)	2	96.50 (15.50)	2	97.00 (15.00)
	14	2	34.50 (0.50)	2	29.50 (2.50)	2	97.50 (1.50)	2	100.00 (17.00)	2	100.00 (17.00)
	15	2	35.00 (1.00)	2	23.50 (8.50)	2	96.50 (1.50)	2	95.00 (11.00)	2	96.00 (10.00)
	16	2	34.50 (0.50)	2	21.50 (9.50)	2	96.50 (1.50)	2	82.00 (0.00)	2	138.00 (56.00)
	17	2	32.00 (1.00)	2	22.50 (9.50)	2	97.50 (0.50)	2	83.50 (2.50)	2	87.50 (6.50)
	18	2	35.00 (1.00)	2	29.50 (2.50)	2	96.50 (2.50)	2	93.00 (12.00)	2	91.00 (10.00)
	19	2	35.50 (0.50)	2	30.00 (2.00)	2	94.50 (0.50)	2	117.50 (31.50)	2	108.50 (23.50)
	20	2	35.00 (1.00)	2	30.00 (2.00)	2	98.00 (2.00)	2	104.50 (24.50)	2	105.00 (25.00)
	21	2	34.50 (1.50)	2	27.00 (0.00)	2	96.50 (0.50)	2	100.50 (18.50)	2	98.00 (16.00)
	22	2	34.00 (1.00)	2	29.50 (2.50)	2	96.50 (1.50)	2	97.50 (13.50)	2	97.00 (13.00)
	23	2	34.00 (1.00)	2	29.00 (2.00)	2	99.50 (0.50)	2	96.50 (10.50)	2	97.00 (11.00)
	24	2	34.50 (1.50)	2	29.50 (2.50)	2	97.00 (3.00)	2	93.00 (19.00)	2	92.00 (18.00)
	25	2	33.00 (1.00)	2	29.50 (2.50)	2	97.50 (0.50)	2	90.50 (16.50)	2	90.00 (16.00)
	26	2	33.00 (0.00)	2	29.00 (2.00)	2	96.50 (1.50)	2	92.50 (14.50)	2	92.00 (14.00)
	27	2	36.00 (0.00)	2	29.00 (3.00)	2	93.50 (4.50)	2	102.00 (21.00)	2	101.50 (20.50)
	28	2	32.00 (0.00)	2	29.00 (3.00)	2	96.50 (1.50)	2	81.00 (5.00)	2	81.50 (4.50)
	29	2	30.50 (0.50)	2	29.00 (3.00)	2	96.50 (1.50)	2	80.50 (7.50)	2	77.00 (4.00)
	30	2	32.00 (1.00)	2	29.00 (3.00)	2	96.50 (0.50)	2	75.00 (1.00)	2	75.00 (1.00)
	31	2	30.50 (0.50)	2	29.00 (3.00)	2	97.00 (2.00)	2	78.00 (3.00)	2	77.50 (2.50)
	32	2	32.00 (0.00)	2	28.50 (2.50)	2	98.50 (0.50)	2	73.50 (3.50)	2	73.00 (3.00)
	33	2	30.00 (1.00)	2	30.00 (2.00)	2	98.00 (0.00)	2	72.50 (3.50)	2	72.50 (3.50)
	34	2	31.50 (0.50)	2	30.00 (2.00)	2	95.50 (2.50)	2	73.00 (1.00)	2	73.00 (1.00)
	35	2	31.50 (0.50)	2	30.00 (2.00)	2	94.50 (3.50)	2	74.50 (1.50)	2	74.00 (2.00)
	36	2	32.00 (2.00)	2	29.50 (1.50)	2	96.75 (0.25)	2	74.00 (2.00)	2	73.75 (1.75)
	37	2	30.00 (4.00)	2	29.00 (3.00)	2	96.00 (4.00)	2	72.00 (0.00)	2	72.00 (0.00)
	38	2	30.50 (1.50)	2	27.00 (5.00)	2	93.50 (2.50)	2	76.50 (3.50)	2	77.00 (4.00)
	39	2	31.50 (1.50)	1	32.00 (n/a)	2	95.00 (4.00)	2	83.00 (10.00)	2	84.00 (11.00)
	40	2	29.00 (0.00)	1	32.00 (n/a)	2	96.50 (0.50)	2	81.50 (12.50)	2	81.00 (12.00)
	41	2	29.50 (0.50)	1	32.00 (n/a)	2	97.00 (1.00)	2	76.50 (7.50)	2	76.50 (7.50)
	42	2	31.00 (2.00)	1	32.00 (n/a)	2	96.00 (2.00)	2	76.00 (2.00)	2	76.00 (2.00)
	43	2	30.50 (2.50)	1	32.00 (n/a)	2	94.00 (1.00)	2	78.00 (2.00)	2	78.50 (2.50)
	44	2	29.00 (2.00)	1	32.00 (n/a)	2	96.50 (0.50)	1	68.00 (n/a)	2	76.50 (8.50)
	45	2	29.00 (3.00)	2	32.00 (0.00)	2	97.00 (3.00)	2	70.50 (3.50)	2	70.00 (3.00)
	46	2	29.50 (1.50)	2	32.50 (0.50)	2	95.00 (1.00)	2	69.50 (0.50)	2	72.00 (3.00)
	47	2	28.50 (2.50)	2	32.50 (0.50)	2	95.00 (2.00)	2	72.00 (1.00)	2	71.50 (0.50)
	48	2	28.50 (2.50)	2	32.50 (0.50)	2	92.50 (3.50)	2	73.00 (0.00)	2	86.50 (13.50)
	49	2	30.50 (5.50)	2	30.00 (0.00)	2	93.00 (3.00)	2	80.50 (8.50)	2	80.50 (8.50)
	50	2	29.50 (3.50)	2	32.50 (0.50)	2	92.50 (0.50)	2	83.00 (14.00)	2	82.50 (14.50)
	51	2	28.00 (3.00)	2	32.50 (0.50)	2	88.00 (2.00)	2	83.00 (10.00)	1	75.00 (n/a)
	52	2	28.00 (3.00)	2	32.50 (0.50)	2	89.50 (1.50)	2	82.00 (6.00)	2	79.00 (4.00)
	53	2	28.50 (2.50)	2	31.50 (1.50)	2	95.00 (1.00)	1	88.00 (n/a)	2	84.50 (4.50)

Table A2a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Pulse Rate by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/NAC (Cont'd)	54	2	30.50 (3.50)	2	32.50 (0.50)	2	92.50 (3.50)	2	85.00 (15.00)	2	85.00 (15.00)
	55	2	29.50 (3.50)	2	32.50 (0.50)	2	90.50 (3.50)	1	77.00 (n/a)	2	84.50 (7.50)
	56	2	30.00 (5.00)	2	32.00 (1.00)	2	93.00 (4.00)	2	74.00 (9.00)	2	74.00 (9.00)
	57	2	32.50 (6.50)	2	32.00 (1.00)	2	87.50 (2.50)	2	82.00 (3.00)	2	81.00 (2.00)
	58	2	31.00 (5.00)	2	32.00 (1.00)	2	94.00 (3.00)	2	76.50 (9.50)	2	77.00 (9.00)
	59	2	30.00 (5.00)	2	32.50 (0.50)	2	94.00 (5.00)	2	78.50 (9.50)	2	79.00 (9.00)
	60	2	32.00 (6.00)	2	32.00 (1.00)	2	94.50 (4.50)	2	88.00 (0.00)	2	83.50 (4.50)
	61	2	33.50 (7.50)	2	31.00 (1.00)	2	93.00 (3.00)	2	90.50 (9.50)	2	91.00 (9.00)
	62	2	34.00 (7.00)	2	32.00 (0.00)	2	91.00 (6.00)	2	101.50 (21.50)	2	100.50 (22.50)
	63	2	34.00 (7.00)	2	32.00 (1.00)	2	90.50 (4.50)	2	99.00 (18.00)	2	99.00 (18.00)
	64	2	32.00 (5.00)	2	31.50 (0.50)	2	94.50 (3.50)	2	97.00 (12.00)	2	96.00 (11.00)
	65	2	31.00 (5.00)	2	31.50 (0.50)	2	92.50 (5.50)	2	86.50 (10.50)	2	87.50 (11.50)
	66	2	31.50 (5.50)	2	32.00 (0.00)	2	93.50 (3.50)	2	94.50 (17.50)	2	94.00 (17.00)
	67	2	31.00 (5.00)	2	32.50 (0.50)	2	94.00 (3.00)	2	91.00 (13.00)	2	91.50 (13.50)
	68	2	31.00 (5.00)	2	32.50 (0.50)	2	96.50 (0.50)	2	88.50 (10.50)	2	86.00 (8.00)
	69	2	28.00 (3.00)	2	32.50 (0.50)	2	98.00 (2.00)	2	74.00 (1.00)	2	70.50 (1.50)
	70	2	28.50 (2.50)	2	32.00 (1.00)	2	97.00 (1.00)	2	75.00 (1.00)	2	71.50 (3.50)
	71	2	28.00 (3.00)	2	31.50 (0.50)	2	98.50 (0.50)	2	69.50 (3.50)	2	69.00 (4.00)
Air/None	0	6	34.00 (1.53)	6	30.67 (0.84)	6	99.67 (0.21)	5	132.20 (14.16)	6	100.67 (7.75)
	1	6	33.83 (1.64)	6	31.17 (0.65)	6	99.83 (0.17)	5	113.60 (16.84)	6	104.17 (9.11)
	2	6	37.00 (2.22)	6	30.67 (0.67)	6	98.17 (1.64)	5	101.20 (7.91)	6	103.83 (6.56)
	3	6	39.67 (2.03)	6	30.67 (0.88)	6	98.83 (0.54)	4	111.00 (15.29)	6	108.83 (9.80)
	4	6	39.83 (2.09)	6	30.33 (1.23)	6	98.67 (0.88)	3	109.00 (8.39)	6	102.67 (5.66)
	5	6	38.17 (1.68)	6	30.50 (0.92)	6	98.83 (0.54)	2	110.00 (4.00)	6	100.00 (5.79)
	6	6	38.50 (1.93)	6	30.33 (0.95)	6	98.83 (0.48)	3	104.33 (3.33)	6	97.83 (3.93)
	7	5	39.80 (2.60)	5	30.80 (1.07)	5	99.80 (0.20)	3	126.00 (13.28)	5	120.60 (9.57)
	8	6	38.67 (1.58)	6	29.83 (0.17)	6	99.50 (0.34)	2	112.50 (8.50)	6	106.67 (5.16)
	9	6	37.83 (1.66)	6	29.83 (0.17)	6	99.50 (0.34)	4	100.75 (3.47)	6	102.33 (2.32)
	10	6	37.83 (1.66)	6	29.67 (0.21)	6	99.17 (0.54)	4	98.00 (7.71)	6	104.83 (3.28)
	11	6	37.50 (1.96)	6	29.67 (0.21)	6	99.00 (0.45)	5	110.00 (12.39)	6	111.67 (8.60)
	12	6	37.83 (1.85)	6	29.83 (0.31)	6	99.50 (0.34)	4	107.25 (8.67)	6	116.33 (7.50)
	13	6	37.00 (1.77)	6	29.83 (0.31)	6	97.50 (1.36)	5	111.60 (7.03)	6	113.67 (7.39)
	14	6	36.67 (1.41)	6	29.67 (0.21)	6	99.00 (0.37)	5	104.20 (10.08)	6	109.50 (5.97)
	15	6	36.83 (1.70)	6	29.33 (0.56)	6	96.83 (1.28)	5	104.00 (9.07)	6	107.50 (7.91)
	16	6	35.33 (1.26)	6	29.67 (0.21)	6	99.50 (0.50)	5	97.80 (5.89)	6	100.50 (5.04)
	17	6	34.33 (1.41)	6	29.67 (0.21)	6	98.67 (0.49)	5	93.80 (4.85)	6	98.67 (4.15)
	18	6	35.00 (1.06)	6	29.67 (0.21)	6	98.17 (0.70)	4	98.25 (8.77)	6	100.33 (6.34)
	19	6	34.67 (0.92)	6	29.83 (0.17)	6	97.33 (0.95)	5	86.20 (7.55)	6	97.33 (6.46)
	20	6	35.00 (1.13)	6	30.17 (0.40)	6	98.33 (0.92)	5	92.40 (7.38)	6	96.50 (6.63)
	21	6	34.50 (1.20)	6	30.17 (0.40)	6	97.50 (1.91)	5	96.60 (6.45)	6	96.83 (4.90)
	22	6	35.50 (1.20)	6	29.83 (0.54)	6	96.50 (1.26)	5	89.40 (7.05)	6	92.17 (6.08)
	23	6	33.67 (1.48)	6	30.00 (0.45)	6	97.00 (1.03)	4	83.50 (9.95)	6	92.67 (6.42)

Table A2a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Pulse Rate by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/None (Cont'd)	24	6	33.83 (0.95)	6	30.00 (0.45)	6	98.50 (0.56)	5	94.80 (4.48)	6	96.67 (3.00)
	25	6	32.67 (1.26)	6	30.17 (0.40)	6	98.83 (0.65)	5	86.00 (3.54)	6	93.17 (5.30)
	26	6	33.17 (1.08)	6	29.83 (0.54)	6	94.33 (2.73)	6	91.00 (8.27)	6	92.33 (7.75)
	27	6	33.83 (1.33)	6	29.83 (0.54)	6	97.00 (1.06)	5	91.20 (6.49)	6	92.50 (5.21)
	28	6	34.33 (1.98)	6	30.00 (0.52)	6	92.67 (1.80)	4	105.25 (18.67)	6	101.33 (10.49)
	29	6	33.33 (2.16)	6	30.17 (0.54)	6	96.50 (1.77)	5	89.60 (3.41)	6	101.33 (12.06)
	30	6	33.33 (1.50)	6	29.33 (0.56)	6	96.83 (1.17)	6	85.67 (3.71)	6	86.83 (3.29)
	31	5	33.00 (1.82)	5	29.60 (0.68)	5	97.60 (1.29)	5	86.40 (8.35)	5	87.60 (7.29)
	32	6	33.50 (1.86)	6	29.67 (0.67)	6	93.83 (2.15)	6	94.92 (5.05)	6	95.33 (4.59)
	33	6	33.00 (1.44)	6	29.83 (0.70)	6	97.00 (1.13)	6	88.33 (4.64)	6	88.33 (4.75)
	34	6	34.83 (1.35)	6	29.50 (0.62)	6	95.00 (1.26)	6	96.50 (4.51)	6	97.33 (5.00)
	35	6	33.17 (1.58)	6	29.67 (0.67)	6	97.67 (0.76)	6	87.33 (6.60)	6	87.67 (6.67)
	36	6	33.00 (1.69)	6	29.83 (0.65)	6	93.83 (1.90)	5	95.40 (8.12)	6	96.00 (9.08)
	37	6	31.17 (1.08)	6	29.83 (0.65)	6	99.17 (0.48)	6	81.50 (4.17)	6	81.67 (4.03)
	38	6	32.83 (1.19)	6	29.83 (0.65)	6	98.00 (0.77)	5	94.60 (8.96)	6	89.67 (7.22)
	39	6	32.83 (1.38)	6	30.00 (0.68)	6	94.17 (1.05)	5	101.00 (7.35)	6	96.50 (7.27)
	40	6	32.83 (1.25)	6	30.00 (0.68)	6	95.50 (1.84)	6	95.83 (6.15)	6	95.83 (6.01)
	41	6	31.83 (1.08)	6	30.00 (0.68)	6	97.17 (1.01)	6	86.67 (4.95)	6	86.83 (5.08)
	42	6	31.67 (1.23)	6	29.67 (0.56)	6	96.83 (1.08)	4	96.00 (9.65)	6	89.50 (6.69)
	43	6	31.67 (1.20)	6	29.67 (0.56)	6	97.50 (1.54)	4	84.75 (2.36)	6	82.33 (2.35)
	44	6	31.17 (0.79)	6	30.00 (0.68)	6	97.50 (0.85)	6	80.17 (3.47)	6	80.83 (3.07)
	45	6	30.50 (1.02)	6	30.00 (0.68)	6	97.67 (1.33)	6	78.67 (2.64)	6	80.00 (2.34)
	46	6	30.17 (1.14)	6	30.00 (0.68)	6	98.17 (0.87)	6	77.17 (4.18)	6	78.17 (3.25)
	47	6	29.67 (1.17)	6	30.00 (0.68)	6	97.33 (1.15)	6	73.67 (3.91)	6	84.17 (9.92)
	48	6	30.33 (1.50)	6	29.83 (0.70)	6	96.17 (1.33)	5	77.80 (2.89)	5	78.40 (2.69)
	49	6	30.50 (1.89)	6	30.00 (0.68)	6	94.33 (1.74)	6	80.50 (6.96)	6	82.33 (5.98)
	50	5	30.40 (2.34)	5	29.80 (0.80)	5	95.60 (1.81)	5	80.40 (6.47)	5	84.00 (6.27)
	51	6	30.67 (1.45)	6	29.83 (0.83)	6	96.50 (1.18)	5	79.60 (2.73)	5	80.40 (2.18)
	52	6	30.17 (1.66)	6	30.00 (0.68)	6	97.67 (0.92)	5	81.20 (2.63)	6	80.33 (2.91)
	53	6	29.50 (1.12)	6	30.00 (0.68)	6	97.00 (1.46)	5	79.20 (4.28)	5	77.60 (4.13)
	54	6	30.83 (1.90)	6	29.83 (0.60)	6	97.83 (1.14)	4	81.25 (3.77)	6	88.00 (9.02)
	55	6	30.00 (1.86)	6	29.83 (0.60)	6	98.50 (1.15)	5	75.40 (2.89)	6	83.83 (8.56)
	56	6	30.33 (2.54)	6	29.83 (0.83)	6	94.17 (2.60)	5	84.00 (7.66)	6	97.00 (16.37)
	57	6	29.67 (1.98)	6	29.83 (0.83)	6	98.33 (0.92)	5	74.20 (2.80)	6	73.83 (2.27)
	58	5	30.00 (2.21)	5	29.40 (0.87)	5	99.00 (0.63)	4	88.25 (6.68)	5	84.40 (5.56)
	59	4	28.25 (1.89)	4	29.00 (1.08)	4	97.50 (1.89)	3	81.33 (11.92)	4	80.25 (8.78)
	60	6	29.50 (1.59)	6	29.67 (0.84)	6	96.00 (1.69)	6	73.50 (1.41)	5	75.00 (2.47)
	61	6	29.33 (1.23)	6	29.50 (0.81)	6	96.00 (1.53)	6	72.83 (2.80)	6	74.83 (4.34)
	62	6	30.33 (1.33)	6	29.50 (0.81)	6	97.50 (0.76)	5	73.20 (1.59)	6	75.83 (2.30)
	63	6	30.33 (1.33)	6	29.33 (0.80)	6	95.67 (0.80)	5	80.00 (3.58)	6	79.00 (4.43)
	64	6	30.33 (1.54)	6	29.17 (0.70)	6	97.67 (0.21)	6	81.67 (4.37)	6	82.33 (4.05)
	65	6	29.33 (1.67)	6	29.67 (0.56)	6	97.00 (0.93)	6	75.83 (3.63)	6	77.17 (2.91)

Table A2a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Pulse Rate by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/None (Cont'd)	66	6	28.83 (1.89)	6	29.67 (0.33)	6	98.50 (0.62)	5	72.40 (4.27)	6	74.33 (3.23)
	67	6	28.83 (1.60)	6	29.83 (0.48)	6	97.00 (1.67)	6	70.83 (2.18)	6	71.50 (1.98)
	68	6	29.00 (1.86)	6	29.67 (0.56)	6	97.00 (1.03)	6	77.17 (3.49)	6	77.17 (3.49)
	69	6	28.00 (1.32)	6	29.83 (0.48)	6	96.50 (1.18)	6	71.00 (2.19)	6	72.33 (3.45)
	70	6	29.33 (1.76)	6	29.83 (0.48)	6	95.83 (1.70)	6	75.83 (6.45)	6	76.33 (6.34)
	71	6	28.83 (1.64)	6	29.83 (0.54)	6	85.50 (11.19)	5	75.00 (6.88)	6	77.83 (5.76)
	72	2	29.67 (1.67)	2	29.83 (0.83)	2	97.00 (0.00)	2	73.83 (1.17)	2	73.50 (1.50)
CG/IBU	0	6	34.17 (1.68)	6	30.00 (0.52)	6	94.00 (1.21)	6	97.00 (8.50)	6	97.50 (8.75)
	1	5	36.60 (1.75)	5	29.40 (0.68)	5	88.80 (3.73)	4	88.75 (6.13)	5	92.00 (8.32)
	2	5	41.60 (2.20)	5	29.80 (0.58)	5	88.20 (1.59)	3	103.67 (4.67)	5	100.00 (6.00)
	3	5	43.40 (1.86)	5	29.80 (0.58)	5	93.20 (1.16)	4	93.50 (4.37)	5	97.20 (6.09)
	4	5	45.80 (2.52)	5	30.20 (0.58)	5	92.20 (1.16)	3	99.00 (7.21)	5	107.20 (6.69)
	5	5	45.80 (2.63)	5	29.40 (0.60)	5	93.80 (1.28)	1	109.00 (n/a)	5	110.80 (5.92)
	6	5	55.00 (3.27)	5	29.80 (0.66)	5	79.40 (2.42)	4	181.50 (29.07)	5	194.20 (26.25)
	7	4	55.75 (3.33)	4	30.00 (0.82)	4	86.50 (1.19)	2	174.00 (52.00)	4	218.00 (33.05)
	8	3	55.33 (6.17)	3	30.00 (1.15)	3	87.00 (2.89)	1	109.00 (n/a)	3	191.67 (43.64)
	9	3	54.00 (6.11)	3	30.00 (1.15)	3	88.67 (3.48)	3	191.67 (42.08)	3	184.33 (37.00)
	10	3	62.67 (8.41)	3	29.33 (0.88)	3	81.00 (3.06)	3	188.33 (31.97)	3	185.67 (30.05)
	11	3	55.33 (3.67)	3	29.67 (0.88)	3	84.33 (2.33)	3	182.67 (17.03)	3	188.00 (22.28)
	12	2	56.50 (9.50)	2	29.00 (1.00)	2	74.50 (11.50)	2	181.00 (26.00)	2	191.00 (43.00)
	13	3	45.33 (8.45)	3	28.67 (0.67)	3	87.67 (5.24)	2	171.00 (49.00)	3	140.67 (39.48)
	14	3	45.33 (7.51)	3	28.67 (0.67)	3	85.33 (6.39)	3	143.33 (35.65)	3	141.33 (34.42)
	15	3	44.67 (6.06)	3	28.67 (0.67)	3	89.00 (5.86)	3	142.33 (32.05)	3	138.33 (28.49)
	16	3	43.67 (6.89)	3	28.67 (0.67)	3	91.67 (4.67)	2	151.50 (38.50)	3	132.67 (27.51)
	17	3	43.67 (6.17)	3	29.00 (0.58)	3	91.33 (5.36)	3	122.67 (27.20)	3	123.33 (25.34)
	18	3	45.00 (4.58)	3	28.67 (0.67)	3	89.00 (5.51)	3	137.33 (15.88)	3	138.00 (16.74)
	19	3	45.00 (5.29)	3	29.00 (1.00)	3	91.33 (4.33)	3	143.67 (23.57)	3	139.67 (19.10)
	20	3	44.33 (6.44)	3	29.00 (0.58)	3	90.33 (5.24)	3	132.00 (25.87)	3	128.33 (22.26)
	21	3	44.00 (6.66)	3	29.33 (0.33)	3	93.00 (3.61)	3	136.00 (29.57)	3	132.67 (26.72)
	22	3	45.00 (4.36)	3	30.00 (1.15)	3	91.33 (4.10)	3	134.33 (12.84)	3	131.00 (10.50)
	23	3	46.00 (3.21)	3	32.33 (2.96)	3	91.67 (2.60)	3	141.33 (9.53)	3	135.00 (5.86)
	24	2	46.00 (3.00)	2	33.00 (5.00)	2	88.50 (0.50)	2	136.00 (10.00)	2	136.00 (11.00)
	25	3	45.33 (2.85)	3	32.33 (2.96)	3	93.67 (2.03)	3	128.00 (9.87)	3	106.33 (15.94)
	26	3	51.00 (9.71)	3	31.67 (1.76)	3	72.00 (16.64)	3	143.67 (12.13)	3	143.33 (12.41)
	27	3	47.33 (4.67)	3	32.00 (2.08)	3	89.33 (3.71)	3	153.33 (21.36)	3	152.67 (21.70)
	28	2	44.00 (5.00)	2	30.00 (1.00)	2	87.50 (6.50)	2	158.00 (4.00)	2	157.00 (5.00)
	29	2	42.00 (5.00)	2	30.50 (1.50)	2	92.00 (7.00)	2	134.50 (6.50)	2	134.00 (6.00)
	30	2	45.00 (10.00)	2	30.50 (1.50)	2	91.50 (7.50)	2	135.00 (13.00)	2	135.00 (14.00)
	31	2	44.00 (7.00)	2	36.50 (5.50)	2	93.00 (1.00)	1	157.00 (n/a)	2	134.50 (19.50)
	32	2	44.50 (9.50)	2	31.50 (0.50)	2	90.00 (6.00)	1	184.00 (n/a)	2	149.50 (32.50)
	33	2	40.50 (5.50)	2	31.00 (0.00)	2	90.00 (8.00)	2	129.50 (7.50)	2	129.50 (8.50)
	34	2	40.00 (6.00)	2	32.00 (0.00)	2	88.00 (10.00)	2	118.00 (3.00)	2	117.00 (2.00)

Table A2a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Pulse Rate by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/IBU (Cont'd)	35	2	43.50 (10.50)	2	31.50 (0.50)	2	88.00 (8.00)	2	122.50 (23.50)	2	124.00 (25.00)
	36	2	41.50 (6.50)	2	32.00 (0.00)	2	90.50 (6.50)	2	119.00 (13.00)	2	128.50 (22.50)
	37	2	41.00 (6.00)	2	32.00 (0.00)	2	87.50 (11.50)	2	114.50 (7.50)	2	113.50 (6.50)
	38	2	40.00 (6.00)	2	31.00 (1.00)	2	87.00 (10.00)	2	115.00 (2.00)	2	116.00 (3.00)
	39	2	42.00 (6.00)	2	31.00 (0.00)	2	85.00 (13.00)	2	124.50 (2.50)	2	125.00 (1.00)
	40	2	43.00 (8.00)	2	31.50 (0.50)	2	86.00 (14.00)	2	128.00 (6.00)	2	127.50 (5.50)
	41	2	42.00 (5.00)	2	31.50 (0.50)	2	88.00 (11.00)	2	125.00 (4.00)	2	129.50 (0.50)
	42	2	41.00 (6.00)	2	31.00 (1.00)	2	87.00 (9.00)	2	122.50 (13.50)	2	128.50 (8.50)
	43	2	43.00 (8.00)	2	30.50 (1.50)	2	84.50 (11.50)	2	127.00 (2.00)	2	126.50 (2.50)
	44	2	42.50 (8.50)	2	30.50 (1.50)	2	88.00 (11.00)	2	126.50 (2.50)	2	126.50 (2.50)
	45	2	45.00 (5.00)	2	30.00 (1.00)	2	86.50 (8.50)	2	118.00 (3.00)	2	117.00 (3.00)
	46	2	41.00 (8.00)	2	30.00 (1.00)	2	86.00 (14.00)	2	122.00 (2.00)	2	121.50 (2.50)
	47	2	41.50 (9.50)	2	30.50 (1.50)	2	83.50 (14.50)	2	118.00 (1.00)	2	117.50 (0.50)
	48	2	42.00 (10.00)	2	30.00 (1.00)	2	84.00 (15.00)	2	115.00 (13.00)	2	111.50 (9.50)
	49	2	40.50 (7.50)	2	30.50 (1.50)	2	79.00 (17.00)	2	118.50 (2.50)	2	118.50 (2.50)
	50	2	39.00 (9.00)	2	30.50 (1.50)	2	84.50 (12.50)	2	111.50 (13.50)	2	110.50 (12.50)
	51	2	39.50 (6.50)	2	30.00 (1.00)	2	81.50 (18.50)	2	114.00 (8.00)	2	113.50 (7.50)
	52	2	44.50 (6.50)	2	30.00 (1.00)	2	75.00 (13.00)	2	149.50 (4.50)	2	145.00 (4.00)
	53	2	41.00 (6.00)	2	30.50 (1.50)	2	75.50 (13.50)	2	136.00 (2.00)	2	134.00 (4.00)
	54	2	40.00 (11.00)	2	30.00 (1.00)	2	85.50 (14.50)	2	112.50 (23.50)	2	111.50 (22.50)
	55	2	38.50 (9.50)	2	30.50 (1.50)	2	82.50 (17.50)	2	102.50 (23.50)	2	101.50 (22.50)
	56	2	37.00 (10.00)	2	31.00 (1.00)	2	84.50 (15.50)	2	95.50 (23.50)	2	95.00 (24.00)
	57	2	38.50 (11.50)	2	31.00 (1.00)	2	82.00 (17.00)	2	91.50 (19.50)	2	93.00 (21.00)
	58	2	40.50 (13.50)	2	31.00 (1.00)	2	84.00 (15.00)	2	105.50 (36.50)	2	104.50 (35.50)
	59	2	42.50 (13.50)	2	31.00 (1.00)	2	87.50 (12.50)	2	129.00 (54.00)	2	128.50 (50.50)
	60	2	42.50 (13.50)	2	31.00 (1.00)	2	88.00 (11.00)	2	136.50 (49.50)	2	128.00 (41.00)
	61	2	40.00 (9.00)	2	30.50 (1.50)	2	69.00 (25.00)	2	113.50 (15.50)	2	112.00 (17.00)
	62	2	39.00 (11.00)	2	30.50 (1.50)	2	78.00 (22.00)	2	99.00 (19.00)	2	99.00 (19.00)
	63	2	39.50 (8.50)	2	31.00 (1.00)	2	76.50 (20.50)	2	107.00 (16.00)	2	106.50 (16.50)
	64	2	38.50 (10.50)	2	31.00 (1.00)	2	72.00 (28.00)	2	91.50 (20.50)	2	92.00 (21.00)
	65	2	37.50 (8.50)	2	30.50 (1.50)	2	85.50 (13.50)	2	96.50 (14.50)	2	93.50 (11.50)
	66	2	40.50 (10.50)	2	30.50 (1.50)	2	66.00 (34.00)	2	108.50 (11.50)	2	108.00 (12.00)
	67	2	40.50 (8.50)	2	31.00 (1.00)	2	63.00 (24.00)	2	115.00 (3.00)	2	109.50 (8.50)
	68	2	41.75 (9.25)	2	30.50 (1.50)	2	66.50 (19.50)	2	123.75 (11.25)	2	127.25 (4.75)
	69	1	51.00 (n/a)	1	32.00 (n/a)	1	31.00 (n/a)	1	153.00 (n/a)	1	152.00 (n/a)
	70	2	40.00 (12.00)	2	30.50 (1.50)	2	72.00 (26.00)	2	115.50 (37.50)	2	114.50 (36.50)
	71	2	40.00 (11.00)	2	30.50 (1.50)	1	98.00 (n/a)	2	109.00 (35.00)	1	74.00 (n/a)
	72	1	29.23 (n/a)	1	29.31 (n/a)	1	93.62 (n/a)	1	84.54 (n/a)	1	86.69 (n/a)
CG/NAC	0	3	33.67 (2.03)	3	23.67 (6.89)	3	98.00 (2.00)	1	87.00 (n/a)	3	90.00 (10.21)
	1	3	39.33 (4.10)	3	25.33 (2.60)	3	96.67 (2.03)	2	76.50 (4.50)	3	84.67 (9.60)
	2	2	42.00 (3.00)	2	30.00 (1.00)	2	95.50 (2.50)	2	81.00 (1.00)	2	81.00 (1.00)
	3	3	39.67 (2.73)	3	30.33 (1.45)	3	97.33 (0.67)	2	88.00 (11.00)	3	88.67 (6.74)

Table A2a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Pulse Rate by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/NAC (Cont'd)	4	2	42.50 (5.50)	2	29.50 (0.50)	2	98.00 (0.00)	1	107.00 (n/a)	2	104.00 (4.00)
	5	2	45.50 (7.50)	2	29.50 (0.50)	2	94.00 (5.00)	1	217.00 (n/a)	2	163.00 (55.00)
	6	2	48.00 (8.00)	2	29.50 (0.50)	2	95.00 (1.00)	1	245.00 (n/a)	2	174.00 (59.00)
	7	2	46.75 (4.75)	2	29.50 (0.50)	2	91.50 (6.50)	1	160.50 (n/a)	2	142.25 (22.25)
	8	1	44.00 (n/a)	1	29.00 (n/a)	1	93.00 (n/a)	0	n/a (n/a)	1	137.00 (n/a)
	9	2	52.50 (7.50)	2	33.00 (5.00)	2	84.00 (10.00)	0	n/a (n/a)	2	197.00 (58.00)
	10	2	50.00 (7.00)	2	28.50 (1.50)	2	84.00 (8.00)	1	200.00 (n/a)	2	196.50 (31.50)
	11	2	50.50 (7.50)	2	29.00 (1.00)	2	84.00 (11.00)	1	130.00 (n/a)	2	139.00 (22.00)
	12	2	51.00 (9.00)	2	29.00 (1.00)	2	82.00 (12.00)	1	230.00 (n/a)	2	184.00 (43.00)
	13	1	42.00 (n/a)	1	28.00 (n/a)	1	94.00 (n/a)	0	n/a (n/a)	1	142.00 (n/a)
	14	1	38.00 (n/a)	1	27.00 (n/a)	1	89.00 (n/a)	0	n/a (n/a)	1	126.00 (n/a)
	15	1	40.00 (n/a)	1	28.00 (n/a)	1	93.00 (n/a)	0	n/a (n/a)	1	129.00 (n/a)
	16	1	36.00 (n/a)	1	27.00 (n/a)	1	97.00 (n/a)	0	n/a (n/a)	1	126.00 (n/a)
	17	1	40.00 (n/a)	1	28.00 (n/a)	1	95.00 (n/a)	0	n/a (n/a)	1	128.00 (n/a)
	18	1	37.00 (n/a)	1	27.00 (n/a)	1	94.00 (n/a)	0	n/a (n/a)	1	123.00 (n/a)
	19	1	37.00 (n/a)	1	28.00 (n/a)	1	97.00 (n/a)	0	n/a (n/a)	1	117.00 (n/a)
	20	1	36.00 (n/a)	1	27.00 (n/a)	1	92.00 (n/a)	0	n/a (n/a)	1	114.00 (n/a)
	21	1	35.00 (n/a)	1	27.00 (n/a)	1	96.00 (n/a)	0	n/a (n/a)	1	114.00 (n/a)
	22	1	37.00 (n/a)	1	27.00 (n/a)	1	93.00 (n/a)	0	n/a (n/a)	1	110.00 (n/a)
	23	1	36.00 (n/a)	1	27.00 (n/a)	1	95.00 (n/a)	0	n/a (n/a)	1	112.00 (n/a)
	24	1	34.00 (n/a)	1	27.00 (n/a)	1	93.00 (n/a)	0	n/a (n/a)	1	103.00 (n/a)
	25	1	32.50 (n/a)	1	26.50 (n/a)	1	95.50 (n/a)	0	n/a (n/a)	1	96.50 (n/a)
	27	1	33.00 (n/a)	1	26.00 (n/a)	1	94.00 (n/a)	0	n/a (n/a)	1	100.00 (n/a)
	28	1	33.00 (n/a)	1	26.00 (n/a)	1	90.00 (n/a)	0	n/a (n/a)	1	102.00 (n/a)
	29	1	33.00 (n/a)	1	26.00 (n/a)	1	92.00 (n/a)	0	n/a (n/a)	1	103.00 (n/a)
	30	1	35.00 (n/a)	1	27.00 (n/a)	1	96.00 (n/a)	0	n/a (n/a)	1	102.00 (n/a)
	31	1	35.00 (n/a)	1	27.00 (n/a)	1	93.00 (n/a)	0	n/a (n/a)	1	99.00 (n/a)
	32	1	35.00 (n/a)	1	27.00 (n/a)	1	93.00 (n/a)	0	n/a (n/a)	1	97.50 (n/a)
	33	1	35.00 (n/a)	1	27.00 (n/a)	1	97.00 (n/a)	0	n/a (n/a)	1	96.00 (n/a)
	34	1	37.00 (n/a)	1	27.00 (n/a)	1	97.00 (n/a)	0	n/a (n/a)	1	92.00 (n/a)
	35	1	32.00 (n/a)	1	27.00 (n/a)	1	97.00 (n/a)	0	n/a (n/a)	1	92.00 (n/a)
	36	1	31.00 (n/a)	1	27.00 (n/a)	1	95.00 (n/a)	0	n/a (n/a)	1	112.00 (n/a)
	37	1	32.00 (n/a)	1	27.00 (n/a)	1	94.00 (n/a)	0	n/a (n/a)	1	93.00 (n/a)
	38	1	31.00 (n/a)	1	27.00 (n/a)	1	93.00 (n/a)	0	n/a (n/a)	1	95.00 (n/a)
	39	1	33.00 (n/a)	1	27.00 (n/a)	1	98.00 (n/a)	0	n/a (n/a)	1	98.00 (n/a)
	40	1	30.00 (n/a)	1	27.00 (n/a)	1	92.00 (n/a)	0	n/a (n/a)	1	90.00 (n/a)
	41	1	33.00 (n/a)	1	27.00 (n/a)	1	92.00 (n/a)	0	n/a (n/a)	1	95.00 (n/a)
	42	1	38.00 (n/a)	1	27.00 (n/a)	1	90.00 (n/a)	0	n/a (n/a)	1	91.00 (n/a)
	43	1	32.00 (n/a)	1	27.00 (n/a)	1	98.00 (n/a)	0	n/a (n/a)	1	86.00 (n/a)
	44	1	30.00 (n/a)	1	27.00 (n/a)	1	98.00 (n/a)	0	n/a (n/a)	1	82.00 (n/a)
	45	1	30.00 (n/a)	1	27.00 (n/a)	1	99.00 (n/a)	0	n/a (n/a)	1	82.00 (n/a)
	46	1	28.00 (n/a)	1	26.00 (n/a)	1	99.00 (n/a)	0	n/a (n/a)	1	81.00 (n/a)

Table A2a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Pulse Rate by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/NAC (Cont'd)	47	1	28.00 (n/a)	1	26.00 (n/a)	1	95.00 (n/a)	0	n/a (n/a)	1	75.00 (n/a)
	48	1	28.00 (n/a)	1	26.00 (n/a)	1	99.00 (n/a)	0	n/a (n/a)	1	75.00 (n/a)
	49	1	30.00 (n/a)	1	26.00 (n/a)	1	85.00 (n/a)	0	n/a (n/a)	0	n/a (n/a)
	50	1	29.00 (n/a)	1	27.00 (n/a)	1	100.00 (n/a)	0	n/a (n/a)	1	79.00 (n/a)
	51	1	29.00 (n/a)	1	26.00 (n/a)	1	100.00 (n/a)	0	n/a (n/a)	1	76.00 (n/a)
	52	1	28.00 (n/a)	1	26.00 (n/a)	1	97.00 (n/a)	0	n/a (n/a)	1	78.00 (n/a)
	53	1	28.00 (n/a)	1	26.00 (n/a)	1	96.00 (n/a)	0	n/a (n/a)	1	78.00 (n/a)
	54	1	26.00 (n/a)	1	26.00 (n/a)	1	99.00 (n/a)	0	n/a (n/a)	1	81.00 (n/a)
	55	1	27.00 (n/a)	1	26.00 (n/a)	1	98.00 (n/a)	0	n/a (n/a)	1	76.00 (n/a)
	56	1	26.00 (n/a)	1	26.00 (n/a)	1	94.00 (n/a)	0	n/a (n/a)	1	73.00 (n/a)
	57	1	26.00 (n/a)	1	26.00 (n/a)	1	94.00 (n/a)	0	n/a (n/a)	1	72.00 (n/a)
	58	1	25.00 (n/a)	1	25.00 (n/a)	1	95.00 (n/a)	0	n/a (n/a)	1	66.00 (n/a)
	59	1	26.00 (n/a)	1	26.00 (n/a)	1	93.00 (n/a)	0	n/a (n/a)	1	68.00 (n/a)
	60	1	27.00 (n/a)	1	26.00 (n/a)	1	98.00 (n/a)	0	n/a (n/a)	1	71.00 (n/a)
	61	1	28.00 (n/a)	1	26.00 (n/a)	1	96.00 (n/a)	0	n/a (n/a)	1	74.00 (n/a)
	62	1	36.00 (n/a)	1	26.00 (n/a)	1	83.00 (n/a)	0	n/a (n/a)	1	117.00 (n/a)
	63	1	31.00 (n/a)	1	26.00 (n/a)	1	96.00 (n/a)	0	n/a (n/a)	1	91.00 (n/a)
	64	1	30.00 (n/a)	1	26.00 (n/a)	1	100.00 (n/a)	0	n/a (n/a)	1	83.00 (n/a)
	65	1	28.00 (n/a)	1	27.00 (n/a)	1	98.00 (n/a)	0	n/a (n/a)	1	76.00 (n/a)
	66	1	27.00 (n/a)	1	26.00 (n/a)	1	99.00 (n/a)	0	n/a (n/a)	1	75.00 (n/a)
	67	1	27.00 (n/a)	1	26.00 (n/a)	1	95.00 (n/a)	0	n/a (n/a)	1	74.00 (n/a)
	68	1	28.00 (n/a)	1	26.00 (n/a)	1	93.00 (n/a)	0	n/a (n/a)	1	74.00 (n/a)
	69	1	27.00 (n/a)	1	26.00 (n/a)	1	90.00 (n/a)	0	n/a (n/a)	1	74.00 (n/a)
	70	1	26.00 (n/a)	1	26.00 (n/a)	1	95.00 (n/a)	0	n/a (n/a)	1	75.00 (n/a)
	71	1	28.00 (n/a)	1	25.00 (n/a)	1	87.00 (n/a)	0	n/a (n/a)	1	74.00 (n/a)
	72	1	27.00 (n/a)	1	25.00 (n/a)	1	100.00 (n/a)	0	n/a (n/a)	1	72.00 (n/a)
CG/None	0	5	35.80 (4.68)	5	28.40 (1.89)	5	97.20 (1.32)	2	112.00 (6.00)	5	100.00 (5.26)
	1	6	38.50 (4.26)	6	27.83 (1.42)	6	96.25 (1.06)	3	101.83 (5.92)	6	100.75 (3.46)
	2	6	43.50 (5.31)	6	28.33 (1.54)	6	96.17 (1.05)	3	115.67 (2.03)	6	107.67 (4.48)
	3	6	43.00 (4.68)	6	28.67 (1.61)	6	97.00 (0.97)	3	115.00 (2.65)	6	111.17 (4.58)
	4	6	42.83 (4.53)	6	28.17 (1.51)	6	97.67 (0.67)	3	140.67 (28.59)	6	107.00 (6.59)
	5	6	43.67 (5.07)	6	28.50 (1.57)	6	96.67 (1.58)	3	137.00 (22.19)	6	119.33 (14.08)
	6	6	46.17 (5.67)	6	28.67 (1.61)	6	92.67 (3.16)	5	137.00 (24.37)	6	143.17 (24.93)
	7	6	47.17 (5.78)	6	28.67 (1.61)	6	93.67 (3.62)	4	143.00 (38.24)	6	156.00 (31.79)
	8	5	43.20 (5.35)	5	28.60 (1.94)	5	96.40 (1.72)	3	170.00 (41.63)	5	124.20 (25.98)
	9	4	41.50 (6.56)	4	28.25 (2.43)	4	96.25 (2.17)	4	150.25 (33.09)	4	130.75 (30.23)
	10	5	43.60 (5.14)	5	28.90 (1.99)	5	94.90 (1.87)	5	124.20 (23.26)	5	124.10 (23.32)
	11	5	43.00 (5.86)	5	28.80 (1.96)	5	96.00 (1.05)	4	111.50 (4.84)	5	131.30 (32.21)
	12	5	42.00 (6.46)	5	28.80 (1.96)	5	95.80 (2.06)	5	124.60 (32.63)	5	124.40 (32.49)
	13	3	49.67 (5.24)	3	31.00 (0.00)	3	94.67 (1.45)	2	188.00 (52.00)	3	161.00 (38.19)
	14	3	52.67 (4.84)	3	30.67 (0.33)	3	93.00 (1.53)	3	169.33 (22.23)	3	170.00 (21.36)
	15	3	54.33 (4.26)	3	30.67 (0.33)	3	95.67 (1.33)	2	215.50 (39.50)	3	194.00 (30.79)

Table A2a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Pulse Rate by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/None (Cont'd)	16	3	54.33 (3.84)	3	30.67 (0.33)	3	91.33 (1.20)	2	216.00 (24.00)	3	193.00 (25.12)
	17	3	52.33 (4.98)	3	31.00 (0.58)	3	91.67 (1.20)	2	192.25 (12.25)	3	166.83 (25.27)
	18	3	53.33 (3.53)	3	30.67 (0.33)	3	88.33 (1.33)	3	161.00 (12.22)	3	161.00 (12.90)
	19	3	50.33 (3.38)	3	30.00 (0.58)	3	92.00 (1.00)	3	140.00 (6.81)	3	138.00 (0.58)
	20	2	51.00 (6.00)	2	30.50 (0.50)	2	93.00 (3.00)	1	122.00 (n/a)	2	129.50 (0.50)
	21	2	52.00 (9.00)	2	30.50 (0.50)	2	92.50 (4.50)	2	121.00 (19.00)	2	129.00 (11.00)
	22	2	36.00 (8.00)	2	30.50 (0.50)	2	90.50 (1.50)	1	137.00 (n/a)	1	130.00 (n/a)
	23	1	45.00 (n/a)	1	30.00 (n/a)	1	88.00 (n/a)	1	119.00 (n/a)	1	138.00 (n/a)
	24	1	47.00 (n/a)	1	30.00 (n/a)	1	91.00 (n/a)	0	n/a (n/a)	1	144.00 (n/a)
	25	1	39.00 (n/a)	1	30.00 (n/a)	1	99.00 (n/a)	1	80.00 (n/a)	1	119.00 (n/a)
	26	1	40.00 (n/a)	1	31.00 (n/a)	1	97.00 (n/a)	1	121.00 (n/a)	1	147.00 (n/a)
	27	1	42.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	128.00 (n/a)	1	131.00 (n/a)
	28	1	38.00 (n/a)	1	31.00 (n/a)	1	98.00 (n/a)	1	123.00 (n/a)	1	123.00 (n/a)
	29	1	40.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	0	n/a (n/a)	1	127.00 (n/a)
	30	1	30.00 (n/a)	1	31.00 (n/a)	1	98.00 (n/a)	1	129.00 (n/a)	1	127.00 (n/a)
	31	1	43.00 (n/a)	1	29.00 (n/a)	1	94.00 (n/a)	0	n/a (n/a)	1	126.00 (n/a)
	32	1	37.00 (n/a)	1	32.00 (n/a)	1	96.00 (n/a)	0	n/a (n/a)	1	127.00 (n/a)
	33	1	37.00 (n/a)	1	31.00 (n/a)	1	98.00 (n/a)	0	n/a (n/a)	1	126.00 (n/a)
	34	1	38.00 (n/a)	1	32.00 (n/a)	1	98.00 (n/a)	1	123.00 (n/a)	1	125.00 (n/a)
	35	1	35.00 (n/a)	1	32.00 (n/a)	1	96.00 (n/a)	1	129.00 (n/a)	1	129.00 (n/a)
	36	1	36.00 (n/a)	1	32.00 (n/a)	1	96.00 (n/a)	1	103.00 (n/a)	1	119.00 (n/a)
	37	1	33.00 (n/a)	1	31.00 (n/a)	1	98.00 (n/a)	1	99.00 (n/a)	1	100.00 (n/a)
	38	1	33.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	107.00 (n/a)	1	106.00 (n/a)
	39	1	33.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	102.00 (n/a)	1	103.00 (n/a)
	41	1	32.00 (n/a)	1	31.00 (n/a)	1	98.50 (n/a)	1	102.00 (n/a)	1	103.00 (n/a)
	42	1	32.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	103.00 (n/a)	1	103.00 (n/a)
	43	1	30.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	96.00 (n/a)	1	96.00 (n/a)
	44	1	30.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	103.00 (n/a)	1	103.00 (n/a)
	45	1	30.00 (n/a)	1	31.00 (n/a)	1	98.00 (n/a)	1	99.00 (n/a)	1	106.00 (n/a)
	46	1	30.00 (n/a)	1	31.00 (n/a)	1	98.00 (n/a)	1	105.00 (n/a)	1	106.00 (n/a)
	47	1	28.00 (n/a)	1	31.00 (n/a)	1	97.00 (n/a)	1	105.00 (n/a)	1	108.00 (n/a)
	48	1	29.00 (n/a)	1	31.00 (n/a)	1	95.00 (n/a)	1	96.00 (n/a)	1	94.00 (n/a)
	49	1	28.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	94.00 (n/a)	1	95.00 (n/a)
	50	1	28.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	91.00 (n/a)	1	90.00 (n/a)
	51	1	27.00 (n/a)	1	31.00 (n/a)	1	98.00 (n/a)	1	90.00 (n/a)	1	90.00 (n/a)
	52	1	28.00 (n/a)	1	31.00 (n/a)	1	96.00 (n/a)	1	100.00 (n/a)	1	99.00 (n/a)
	53	1	28.00 (n/a)	1	31.00 (n/a)	1	96.00 (n/a)	1	96.00 (n/a)	1	104.00 (n/a)
	54	1	37.00 (n/a)	1	31.00 (n/a)	1	86.00 (n/a)	1	113.00 (n/a)	1	126.00 (n/a)
	55	1	30.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	92.00 (n/a)	1	90.00 (n/a)
	56	1	28.00 (n/a)	1	30.00 (n/a)	1	95.00 (n/a)	1	90.00 (n/a)	1	90.00 (n/a)
	57	1	29.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	90.00 (n/a)	1	90.00 (n/a)
	58	1	28.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	90.00 (n/a)	1	91.00 (n/a)

Table A2a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Pulse Rate by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/None (Cont'd)	59	1	28.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	84.00 (n/a)	1	83.00 (n/a)
	60	1	27.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	82.00 (n/a)	1	82.00 (n/a)
	61	1	27.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	81.00 (n/a)	1	82.00 (n/a)
	62	1	27.00 (n/a)	1	31.00 (n/a)	1	98.00 (n/a)	1	94.00 (n/a)	1	93.00 (n/a)
	63	1	28.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	100.00 (n/a)	1	100.00 (n/a)
	64	1	28.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	98.00 (n/a)	1	98.00 (n/a)
	65	1	28.00 (n/a)	1	31.00 (n/a)	1	98.00 (n/a)	1	101.00 (n/a)	1	101.00 (n/a)
	66	1	28.00 (n/a)	1	31.00 (n/a)	1	98.00 (n/a)	1	94.00 (n/a)	1	92.00 (n/a)
	67	1	33.00 (n/a)	1	31.00 (n/a)	1	96.00 (n/a)	1	111.00 (n/a)	1	112.00 (n/a)
	68	1	28.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	90.00 (n/a)	1	91.00 (n/a)
	69	1	26.00 (n/a)	1	31.00 (n/a)	1	98.00 (n/a)	1	88.00 (n/a)	1	88.00 (n/a)
	70	1	26.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	93.00 (n/a)	1	96.00 (n/a)
	71	1	24.00 (n/a)	1	31.00 (n/a)	1	99.00 (n/a)	1	95.00 (n/a)	1	95.00 (n/a)
CG/PEEP	0	4	33.00 (1.58)	4	37.00 (4.34)	4	98.50 (0.65)	3	105.33 (17.38)	4	99.50 (13.25)
	1	4	36.63 (1.38)	4	41.00 (4.18)	4	97.38 (1.97)	3	94.50 (11.25)	4	93.13 (6.64)
	2	4	39.00 (1.29)	4	41.50 (3.57)	4	99.50 (0.50)	1	102.00 (n/a)	4	97.25 (2.66)
	3	3	39.33 (4.06)	3	41.33 (5.17)	3	97.67 (1.86)	1	120.00 (n/a)	3	112.00 (8.62)
	4	3	42.00 (3.06)	3	46.33 (0.88)	3	99.33 (0.67)	3	108.33 (17.40)	3	108.33 (18.85)
	5	3	45.33 (2.91)	3	46.33 (0.88)	3	100.00 (0.00)	2	119.50 (21.50)	3	117.00 (11.79)
	6	2	47.50 (0.50)	2	47.00 (1.00)	2	100.00 (0.00)	2	174.50 (22.50)	2	142.00 (18.00)
	7	2	46.00 (2.00)	2	48.50 (2.50)	2	98.50 (1.50)	2	187.00 (18.00)	2	182.50 (22.50)
	8	2	45.50 (0.50)	2	46.00 (2.00)	2	100.00 (0.00)	2	176.00 (9.00)	2	174.00 (10.00)
	9	2	47.00 (0.00)	2	46.00 (2.00)	2	99.00 (1.00)	2	177.50 (2.50)	2	177.50 (2.50)
	10	2	48.00 (0.00)	2	45.50 (0.50)	2	99.00 (1.00)	2	169.50 (10.50)	2	167.50 (12.50)
	11	2	47.50 (0.50)	2	46.00 (1.00)	2	98.50 (1.50)	2	177.50 (5.50)	2	178.00 (0.00)
	12	2	47.50 (0.50)	2	44.50 (2.50)	2	97.50 (2.50)	2	190.00 (7.00)	2	187.00 (5.00)
	13	2	46.00 (2.00)	2	44.00 (3.00)	2	99.50 (0.50)	2	165.00 (18.00)	2	163.00 (16.00)
	14	2	42.50 (5.50)	2	44.50 (2.50)	2	98.50 (1.50)	2	147.50 (14.50)	2	139.50 (22.50)
	15	1	48.00 (n/a)	1	42.00 (n/a)	1	96.00 (n/a)	1	175.00 (n/a)	1	167.00 (n/a)
	16	1	46.00 (n/a)	1	40.00 (n/a)	1	95.00 (n/a)	1	177.00 (n/a)	1	177.00 (n/a)
	17	1	45.00 (n/a)	1	40.00 (n/a)	1	98.00 (n/a)	1	169.00 (n/a)	1	164.00 (n/a)
	18	1	45.00 (n/a)	1	39.00 (n/a)	1	98.00 (n/a)	0	n/a (n/a)	1	144.00 (n/a)
	19	1	45.00 (n/a)	1	39.00 (n/a)	1	97.00 (n/a)	0	n/a (n/a)	1	136.00 (n/a)
	20	1	43.00 (n/a)	1	39.00 (n/a)	1	99.00 (n/a)	1	136.00 (n/a)	1	130.00 (n/a)
	21	1	40.00 (n/a)	1	39.00 (n/a)	1	96.00 (n/a)	1	121.00 (n/a)	1	112.00 (n/a)
	22	1	39.00 (n/a)	1	39.00 (n/a)	1	98.00 (n/a)	1	106.00 (n/a)	1	105.00 (n/a)
	23	1	37.00 (n/a)	1	39.00 (n/a)	1	100.00 (n/a)	1	93.00 (n/a)	1	91.00 (n/a)
	24	1	36.00 (n/a)	1	39.00 (n/a)	1	98.00 (n/a)	1	84.00 (n/a)	1	88.00 (n/a)
	25	1	39.00 (n/a)	1	39.00 (n/a)	1	99.00 (n/a)	1	86.00 (n/a)	1	86.00 (n/a)
	26	1	38.00 (n/a)	1	38.00 (n/a)	1	100.00 (n/a)	1	82.00 (n/a)	1	82.00 (n/a)
	27	1	40.00 (n/a)	1	38.00 (n/a)	1	100.00 (n/a)	1	89.00 (n/a)	1	89.00 (n/a)
	28	1	41.00 (n/a)	1	37.00 (n/a)	1	92.00 (n/a)	1	111.00 (n/a)	1	111.00 (n/a)

Table A2a. Descriptive Statistics for Expired CO_2, Inspired O_2, Oxygen Saturation, Heart Rate, and Pulse Rate by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Expired CO_2 (%)		Inspired O_2 (%)		Oxygen Saturation (%)		Heart Rate (Beats/Minute)		Pulse Rate (Beats/Minute)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/PEEP (Cont'd)	29	1	41.00 (n/a)	1	37.00 (n/a)	1	93.00 (n/a)	1	121.00 (n/a)	1	120.00 (n/a)
	30	1	42.00 (n/a)	1	38.00 (n/a)	1	93.00 (n/a)	0	n/a (n/a)	1	123.00 (n/a)
	31	1	43.00 (n/a)	1	37.00 (n/a)	1	93.00 (n/a)	0	n/a (n/a)	1	125.00 (n/a)
	32	1	45.00 (n/a)	1	38.00 (n/a)	1	88.00 (n/a)	1	129.00 (n/a)	1	121.00 (n/a)
	33	1	46.00 (n/a)	1	38.00 (n/a)	1	88.00 (n/a)	1	126.00 (n/a)	1	125.00 (n/a)
	34	1	46.00 (n/a)	1	38.00 (n/a)	1	88.00 (n/a)	1	115.00 (n/a)	1	115.00 (n/a)
	35	1	43.00 (n/a)	1	39.00 (n/a)	1	94.00 (n/a)	1	110.00 (n/a)	1	110.00 (n/a)
	36	1	43.00 (n/a)	1	38.00 (n/a)	1	82.00 (n/a)	1	111.00 (n/a)	1	110.00 (n/a)
	37	1	41.00 (n/a)	1	39.00 (n/a)	1	87.00 (n/a)	1	104.00 (n/a)	1	103.00 (n/a)
	38	1	41.00 (n/a)	1	39.00 (n/a)	1	90.00 (n/a)	1	95.00 (n/a)	1	96.00 (n/a)
	39	1	39.00 (n/a)	1	39.00 (n/a)	1	98.00 (n/a)	1	85.00 (n/a)	1	85.00 (n/a)
	40	1	39.00 (n/a)	1	38.00 (n/a)	1	99.00 (n/a)	0	n/a (n/a)	1	93.00 (n/a)
	41	1	40.00 (n/a)	1	39.00 (n/a)	1	99.00 (n/a)	0	n/a (n/a)	1	95.00 (n/a)
	42	1	40.00 (n/a)	1	39.00 (n/a)	1	100.00 (n/a)	1	84.00 (n/a)	1	84.00 (n/a)
	43	1	40.00 (n/a)	1	39.00 (n/a)	1	100.00 (n/a)	1	88.00 (n/a)	1	88.00 (n/a)
	44	1	39.00 (n/a)	1	39.00 (n/a)	1	99.00 (n/a)	1	85.00 (n/a)	1	85.00 (n/a)
	45	1	37.00 (n/a)	1	39.00 (n/a)	1	99.00 (n/a)	1	75.00 (n/a)	1	75.00 (n/a)
	46	1	38.00 (n/a)	1	39.00 (n/a)	1	100.00 (n/a)	1	77.00 (n/a)	1	78.00 (n/a)
	47	1	35.00 (n/a)	1	39.00 (n/a)	1	100.00 (n/a)	1	78.00 (n/a)	1	78.00 (n/a)
	48	1	34.00 (n/a)	1	38.00 (n/a)	1	100.00 (n/a)	1	67.00 (n/a)	1	67.00 (n/a)
	49	1	32.00 (n/a)	1	38.00 (n/a)	1	100.00 (n/a)	1	62.00 (n/a)	1	62.00 (n/a)
	50	1	35.00 (n/a)	1	38.00 (n/a)	1	98.00 (n/a)	1	73.00 (n/a)	1	73.00 (n/a)
	51	1	38.00 (n/a)	1	38.00 (n/a)	1	100.00 (n/a)	1	68.00 (n/a)	1	67.00 (n/a)
	52	1	34.00 (n/a)	1	38.00 (n/a)	1	100.00 (n/a)	1	69.00 (n/a)	1	69.00 (n/a)
	53	1	33.00 (n/a)	1	38.00 (n/a)	1	100.00 (n/a)	1	68.00 (n/a)	1	67.00 (n/a)
	54	1	35.00 (n/a)	1	38.00 (n/a)	1	93.00 (n/a)	1	73.00 (n/a)	1	72.00 (n/a)
	55	1	37.00 (n/a)	1	38.00 (n/a)	1	93.00 (n/a)	1	76.00 (n/a)	1	76.00 (n/a)
	56	1	37.00 (n/a)	1	38.00 (n/a)	1	91.00 (n/a)	1	119.00 (n/a)	1	76.00 (n/a)
	57	1	51.00 (n/a)	1	37.00 (n/a)	1	89.00 (n/a)	1	88.00 (n/a)	1	89.00 (n/a)
	58	1	44.00 (n/a)	1	37.00 (n/a)	1	97.00 (n/a)	1	96.00 (n/a)	1	96.00 (n/a)
	59	1	43.00 (n/a)	1	38.00 (n/a)	1	93.00 (n/a)	1	94.00 (n/a)	1	94.00 (n/a)
	60	1	39.00 (n/a)	1	38.00 (n/a)	1	96.00 (n/a)	1	84.00 (n/a)	1	84.00 (n/a)
	61	1	38.00 (n/a)	1	38.00 (n/a)	1	93.00 (n/a)	1	81.00 (n/a)	1	82.00 (n/a)
	62	1	38.00 (n/a)	1	38.00 (n/a)	1	92.00 (n/a)	1	81.00 (n/a)	1	82.00 (n/a)
	63	1	37.00 (n/a)	1	38.00 (n/a)	1	93.00 (n/a)	1	78.00 (n/a)	1	78.00 (n/a)
	64	1	37.00 (n/a)	1	38.00 (n/a)	1	97.00 (n/a)	1	76.00 (n/a)	1	77.00 (n/a)
	65	1	36.00 (n/a)	1	38.00 (n/a)	1	96.00 (n/a)	1	75.00 (n/a)	1	75.00 (n/a)
	66	1	39.00 (n/a)	1	38.00 (n/a)	1	94.00 (n/a)	1	78.00 (n/a)	1	79.00 (n/a)
	67	1	37.00 (n/a)	1	38.00 (n/a)	1	85.00 (n/a)	1	75.00 (n/a)	1	75.00 (n/a)
	68	1	38.00 (n/a)	1	38.00 (n/a)	1	83.00 (n/a)	1	76.00 (n/a)	1	75.00 (n/a)
	69	1	34.00 (n/a)	1	38.00 (n/a)	1	91.00 (n/a)	1	72.00 (n/a)	1	70.00 (n/a)
	70	1	34.00 (n/a)	1	37.00 (n/a)	1	72.00 (n/a)	1	69.00 (n/a)	1	69.00 (n/a)
	71	1	34.00 (n/a)	1	37.00 (n/a)	1	82.00 (n/a)	1	77.00 (n/a)	1	76.00 (n/a)

Table A2b. Descriptive Statistics for Respiratory Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Exposure/Treatment Groups and Study Timecourse.

Group	Study Time-course	Respiratory Rate (Breathes/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/IBU	0	5	15.00 (0.00)	5	21.16 (1.31)	5	94.00 (7.77)	5	59.80 (4.88)	5	74.80 (3.61)
	1	5	15.00 (0.00)	5	22.45 (1.14)	4	97.25 (5.85)	4	67.75 (7.26)	4	80.25 (4.27)
	2	5	15.00 (0.00)	5	21.70 (1.40)	5	97.20 (3.97)	5	63.00 (7.18)	5	78.40 (6.10)
	3	5	15.00 (0.00)	5	21.63 (1.20)	5	95.80 (3.34)	5	58.40 (4.96)	5	72.00 (4.23)
	4	5	15.00 (0.00)	5	21.06 (1.17)	5	78.80 (6.67)	5	51.00 (4.49)	5	59.80 (4.07)
	5	5	15.00 (0.00)	5	20.90 (1.20)	4	67.25 (1.93)	4	43.25 (6.06)	4	50.50 (5.78)
	6	5	15.00 (0.00)	5	21.06 (1.37)	5	78.60 (8.78)	5	54.60 (16.06)	5	62.00 (14.40)
	7	5	15.00 (0.00)	5	20.70 (1.41)	5	87.20 (14.79)	5	57.40 (17.70)	5	67.00 (17.38)
	8	5	15.00 (0.00)	5	20.90 (1.33)	5	76.80 (12.86)	5	51.00 (11.61)	5	63.20 (11.57)
	9	5	15.00 (0.00)	5	20.60 (1.26)	5	76.60 (6.77)	5	49.60 (13.54)	5	56.20 (13.15)
	10	4	15.00 (0.00)	4	20.73 (1.27)	4	82.00 (5.49)	4	54.75 (10.79)	4	65.25 (9.20)
	11	4	15.00 (0.00)	4	20.83 (1.46)	3	81.00 (7.77)	3	38.67 (9.02)	3	50.33 (9.91)
	12	4	15.00 (0.00)	4	20.60 (1.49)	4	72.50 (4.99)	4	51.75 (13.28)	4	58.75 (11.40)
	13	4	15.00 (0.00)	4	20.23 (1.21)	4	71.00 (6.52)	4	52.75 (11.80)	4	57.25 (10.57)
	14	4	15.00 (0.00)	4	20.35 (1.12)	4	73.50 (6.13)	4	42.25 (4.71)	4	52.00 (2.08)
	15	4	15.00 (0.00)	4	20.50 (1.33)	4	80.00 (8.10)	4	44.75 (5.65)	4	55.75 (4.77)
	16	4	15.00 (0.00)	4	20.10 (1.42)	4	80.50 (4.09)	4	48.75 (9.33)	4	62.00 (10.01)
	17	4	15.00 (0.00)	4	19.75 (1.26)	4	91.25 (7.19)	4	67.25 (15.83)	4	72.75 (12.53)
	18	4	15.00 (0.00)	4	20.18 (1.29)	4	84.25 (5.54)	4	37.75 (3.28)	4	52.00 (2.61)
	19	4	15.00 (0.00)	4	20.25 (1.29)	4	76.75 (8.51)	4	38.00 (5.80)	4	49.25 (4.25)
	20	4	15.00 (0.00)	4	19.58 (1.17)	4	66.00 (6.16)	4	38.50 (6.59)	4	49.25 (5.85)
	21	4	15.00 (0.00)	4	19.73 (1.42)	4	74.00 (10.75)	4	51.50 (14.17)	4	58.50 (12.61)
	22	4	15.00 (0.00)	4	19.68 (1.61)	4	65.50 (3.93)	4	41.50 (7.77)	4	49.00 (6.36)
	23	4	15.00 (0.00)	4	19.03 (1.45)	4	63.00 (6.60)	4	34.75 (5.99)	4	44.25 (7.00)
	24	4	15.00 (0.00)	4	19.45 (1.59)	4	65.50 (8.37)	4	39.00 (9.43)	4	47.00 (9.62)
	25	4	15.00 (0.00)	4	18.83 (1.33)	4	75.00 (9.69)	4	45.00 (11.45)	4	62.75 (15.47)
	26	4	15.00 (0.00)	4	18.83 (1.17)	4	74.00 (9.40)	4	40.25 (10.12)	4	50.50 (11.21)
	27	3	15.00 (0.00)	3	18.97 (1.86)	3	86.33 (4.18)	3	46.67 (4.91)	3	60.00 (4.73)
	28	3	15.00 (0.00)	3	18.83 (1.82)	3	90.33 (2.91)	3	72.00 (13.23)	3	78.67 (8.45)
	29	3	15.00 (0.00)	3	18.70 (1.64)	3	110.33 (23.14)	3	97.00 (19.73)	3	100.67 (21.06)
	30	3	15.00 (0.00)	3	18.67 (1.59)	3	114.67 (16.91)	3	92.67 (23.21)	3	102.33 (19.32)
	31	3	15.00 (0.00)	3	18.73 (1.71)	3	95.00 (1.15)	3	75.67 (7.51)	3	83.33 (3.76)
	32	3	15.00 (0.00)	3	18.97 (1.63)	3	93.33 (9.84)	3	70.00 (9.61)	3	79.67 (7.42)
	33	3	15.00 (0.00)	3	18.77 (1.80)	3	89.33 (4.81)	3	74.33 (10.37)	3	80.00 (8.02)
	34	3	15.00 (0.00)	3	18.67 (1.59)	3	83.33 (3.48)	3	55.67 (10.14)	3	66.00 (7.81)
	35	3	15.00 (0.00)	3	18.50 (1.53)	3	88.67 (4.10)	3	54.33 (7.36)	3	66.67 (3.71)
	36	3	15.00 (0.00)	3	18.83 (1.39)	3	97.33 (10.49)	3	53.00 (8.19)	3	66.67 (8.33)
	37	3	15.00 (0.00)	3	18.50 (1.66)	3	91.00 (11.93)	3	52.00 (7.09)	3	61.67 (9.33)
	38	3	15.00 (0.00)	3	17.90 (2.01)	3	84.00 (7.21)	3	53.33 (6.57)	3	63.33 (6.98)

Table A2b. Descriptive Statistics for Respiratory Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Respiratory Rate (Breathes/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/IBU (Cont'd)	39	3	15.00 (0.00)	3	17.53 (1.64)	3	84.33 (6.17)	3	50.33 (10.17)	3	63.00 (8.39)
	40	3	15.00 (0.00)	3	18.07 (1.40)	3	103.33 (3.33)	3	70.00 (11.53)	3	83.67 (6.36)
	41	3	15.00 (0.00)	3	17.93 (1.31)	3	83.67 (7.36)	3	47.33 (2.33)	3	60.00 (1.15)
	42	3	15.00 (0.00)	3	18.07 (1.18)	3	91.00 (9.54)	3	47.00 (5.20)	3	66.67 (7.84)
	43	3	15.00 (0.00)	3	18.47 (1.63)	3	96.00 (13.65)	3	51.33 (9.87)	3	68.67 (12.33)
	44	3	15.00 (0.00)	3	18.07 (1.77)	3	92.00 (15.63)	3	53.67 (5.21)	3	68.00 (8.74)
	45	3	15.00 (0.00)	3	18.30 (1.90)	3	93.67 (10.40)	3	46.00 (6.08)	3	64.00 (8.08)
	46	3	15.00 (0.00)	3	18.57 (1.90)	3	80.67 (11.10)	3	46.67 (0.88)	3	59.00 (4.73)
	47	3	15.00 (0.00)	3	18.27 (1.43)	3	82.67 (15.34)	3	52.33 (3.76)	3	63.67 (7.51)
	48	3	15.00 (0.00)	3	18.73 (2.09)	3	77.00 (10.79)	3	55.67 (2.91)	3	62.67 (4.37)
	49	3	15.00 (0.00)	3	18.57 (2.05)	3	81.67 (12.72)	3	67.67 (12.02)	3	72.67 (11.98)
	50	3	15.00 (0.00)	3	18.40 (2.06)	3	73.33 (9.74)	3	55.67 (5.70)	3	62.00 (6.08)
	51	3	15.00 (0.00)	3	18.07 (1.82)	3	92.00 (12.29)	3	56.67 (0.67)	3	70.33 (4.06)
	52	3	15.00 (0.00)	3	18.27 (1.69)	3	85.00 (14.84)	3	56.67 (2.91)	3	66.67 (5.49)
	53	3	15.00 (0.00)	3	18.37 (1.84)	2	100.00 (13.00)	2	80.50 (12.50)	2	89.00 (11.00)
	54	3	15.00 (0.00)	3	18.20 (1.72)	2	107.50 (5.50)	2	61.50 (6.50)	2	78.50 (5.50)
	55	3	15.00 (0.00)	3	18.63 (1.91)	3	92.33 (20.19)	3	52.00 (5.57)	3	65.67 (9.96)
	56	3	15.00 (0.00)	3	18.43 (2.14)	2	113.50 (0.50)	2	73.00 (22.00)	2	89.00 (12.00)
	57	3	15.00 (0.00)	3	18.57 (1.76)	2	91.00 (13.00)	2	56.00 (7.00)	2	68.00 (1.00)
	58	3	15.00 (0.00)	3	18.57 (2.09)	2	103.50 (3.50)	2	67.50 (14.50)	2	81.00 (8.00)
	59	3	15.00 (0.00)	3	18.80 (2.44)	2	104.00 (8.00)	2	51.00 (9.00)	2	70.00 (10.00)
	60	3	15.00 (0.00)	3	18.50 (2.47)	2	96.50 (0.50)	2	48.50 (6.50)	2	68.00 (7.00)
	61	3	15.00 (0.00)	3	18.10 (2.24)	2	106.50 (17.50)	2	70.50 (26.50)	2	83.00 (24.00)
	62	3	15.00 (0.00)	3	18.60 (1.82)	2	100.50 (8.50)	2	51.50 (6.50)	2	69.00 (8.00)
	63	3	15.00 (0.00)	3	19.27 (2.39)	2	106.00 (9.00)	2	54.50 (9.50)	2	73.50 (10.50)
	64	3	15.00 (0.00)	3	19.40 (2.36)	2	110.50 (20.50)	2	70.00 (27.00)	2	84.50 (25.50)
	65	3	15.00 (0.00)	3	19.70 (2.44)	2	107.00 (0.00)	2	85.50 (12.50)	2	91.50 (6.50)
	66	3	15.00 (0.00)	3	18.77 (2.58)	2	90.50 (1.50)	2	44.00 (3.00)	2	60.50 (2.50)
	67	3	15.00 (0.00)	3	18.97 (2.86)	2	88.50 (3.50)	2	45.50 (1.50)	2	61.00 (2.00)
	68	3	15.00 (0.00)	3	19.47 (2.69)	2	86.50 (0.50)	2	45.00 (2.00)	2	59.00 (1.00)
	69	3	15.00 (0.00)	3	19.30 (2.52)	2	88.00 (1.00)	2	44.50 (1.50)	2	58.50 (1.50)
	70	3	15.00 (0.00)	3	19.17 (2.39)	2	92.00 (1.00)	2	64.00 (17.00)	2	74.00 (11.00)
	71	3	15.00 (0.00)	3	19.57 (2.60)	2	90.50 (1.50)	2	47.00 (1.00)	2	63.00 (1.00)
Air/NAC	0	2	15.00 (0.00)	0	n/a (n/a)	1	81.00 (n/a)	1	49.00 (n/a)	1	61.00 (n/a)
	1	2	15.00 (0.00)	2	23.53 (0.28)	2	87.00 (1.00)	2	56.00 (2.00)	2	69.00 (1.00)
	2	2	15.00 (0.00)	2	21.68 (0.13)	2	95.00 (1.00)	2	53.00 (2.00)	2	69.00 (2.00)
	3	2	15.00 (0.00)	2	21.65 (0.35)	2	86.50 (18.50)	2	60.00 (1.00)	2	69.50 (7.50)
	4	2	15.00 (0.00)	2	20.70 (0.40)	1	71.00 (n/a)	1	38.00 (n/a)	1	49.00 (n/a)
	5	2	15.00 (0.00)	2	21.05 (0.25)	1	91.00 (n/a)	1	50.00 (n/a)	1	64.00 (n/a)
	6	2	15.00 (0.00)	2	21.15 (1.45)	1	74.00 (n/a)	1	36.00 (n/a)	1	48.00 (n/a)
	7	2	15.00 (0.00)	2	21.45 (1.15)	1	102.00 (n/a)	1	59.00 (n/a)	1	76.00 (n/a)

Table A2b. Descriptive Statistics for Respiratory Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Respiratory Rate (Breathes/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/NAC (Cont'd)	8	2	15.00 (0.00)	2	21.60 (0.30)	1	46.00 (n/a)	1	23.00 (n/a)	1	31.00 (n/a)
	9	2	15.00 (0.00)	2	21.05 (0.55)	1	79.00 (n/a)	1	36.00 (n/a)	1	50.00 (n/a)
	10	2	15.00 (0.00)	2	21.15 (1.05)	1	79.00 (n/a)	1	33.00 (n/a)	1	47.00 (n/a)
	11	2	15.00 (0.00)	2	21.25 (0.45)	1	75.00 (n/a)	1	34.00 (n/a)	1	47.00 (n/a)
	12	2	15.00 (0.00)	2	21.05 (0.95)	1	65.00 (n/a)	1	32.00 (n/a)	1	43.00 (n/a)
	13	2	15.00 (0.00)	2	21.40 (0.90)	1	72.00 (n/a)	1	34.00 (n/a)	1	46.00 (n/a)
	14	2	15.00 (0.00)	2	20.40 (1.20)	1	74.00 (n/a)	1	33.00 (n/a)	1	45.00 (n/a)
	15	2	15.00 (0.00)	2	20.35 (1.05)	1	69.00 (n/a)	1	32.00 (n/a)	1	42.00 (n/a)
	16	2	15.00 (0.00)	2	20.20 (1.40)	2	89.50 (29.50)	2	58.50 (13.50)	2	69.00 (20.00)
	17	2	15.00 (0.00)	2	20.45 (0.85)	2	81.50 (21.50)	2	47.00 (8.00)	2	60.00 (15.00)
	18	2	15.00 (0.00)	2	21.25 (1.25)	2	84.00 (19.00)	2	47.50 (8.50)	2	56.00 (16.00)
	19	2	15.00 (0.00)	2	20.80 (1.20)	2	89.50 (26.50)	2	53.00 (20.00)	2	66.00 (23.00)
	20	2	15.00 (0.00)	2	19.95 (0.95)	2	82.50 (17.50)	2	58.00 (20.00)	2	67.00 (19.00)
	21	2	15.00 (0.00)	2	19.55 (1.85)	2	81.50 (1.50)	2	54.50 (5.50)	2	62.00 (2.00)
	22	2	15.00 (0.00)	2	19.65 (0.95)	2	88.00 (21.00)	2	54.50 (13.50)	2	67.00 (17.00)
	23	2	15.00 (0.00)	2	19.50 (0.80)	2	87.50 (12.50)	2	52.50 (3.50)	2	64.50 (7.50)
	24	2	15.00 (0.00)	2	19.75 (1.15)	1	103.00 (n/a)	1	52.00 (n/a)	1	70.00 (n/a)
	25	2	15.00 (0.00)	2	19.85 (1.65)	1	107.00 (n/a)	1	69.00 (n/a)	1	85.00 (n/a)
	26	2	15.00 (0.00)	2	20.20 (0.30)	1	115.00 (n/a)	1	64.00 (n/a)	1	84.00 (n/a)
	27	2	15.00 (0.00)	2	19.35 (1.05)	1	128.00 (n/a)	1	76.00 (n/a)	1	95.00 (n/a)
	28	2	15.00 (0.00)	2	19.55 (0.75)	1	85.00 (n/a)	1	44.00 (n/a)	1	56.00 (n/a)
	29	2	15.00 (0.00)	2	19.85 (0.75)	1	119.00 (n/a)	1	95.00 (n/a)	1	103.00 (n/a)
	30	2	15.00 (0.00)	2	19.30 (1.60)	1	101.00 (n/a)	1	52.00 (n/a)	1	61.00 (n/a)
	31	2	15.00 (0.00)	2	19.20 (1.50)	1	88.00 (n/a)	1	42.00 (n/a)	1	57.00 (n/a)
	32	2	15.00 (0.00)	2	19.00 (0.70)	1	85.00 (n/a)	1	41.00 (n/a)	1	53.00 (n/a)
	33	2	15.00 (0.00)	2	18.70 (0.40)	1	83.00 (n/a)	1	40.00 (n/a)	1	53.00 (n/a)
	34	2	15.00 (0.00)	2	19.40 (1.00)	1	84.00 (n/a)	1	38.00 (n/a)	1	51.00 (n/a)
	35	2	15.00 (0.00)	2	19.40 (0.90)	1	83.00 (n/a)	1	38.00 (n/a)	1	51.00 (n/a)
	36	2	15.00 (0.00)	2	19.25 (0.45)	1	99.50 (n/a)	1	53.00 (n/a)	1	67.50 (n/a)
	37	2	15.00 (0.00)	2	19.65 (0.65)	1	90.00 (n/a)	1	45.00 (n/a)	1	58.00 (n/a)
	38	2	15.00 (0.00)	2	19.10 (0.00)	1	105.00 (n/a)	1	52.00 (n/a)	1	71.00 (n/a)
	39	2	15.00 (0.00)	2	18.95 (0.15)	1	114.00 (n/a)	1	57.00 (n/a)	1	78.00 (n/a)
	40	2	15.00 (0.00)	2	19.35 (0.55)	1	90.00 (n/a)	1	41.00 (n/a)	1	57.00 (n/a)
	41	2	15.00 (0.00)	2	19.55 (0.75)	2	82.00 (23.00)	2	44.00 (5.00)	2	56.50 (11.50)
	42	2	15.00 (0.00)	2	18.85 (0.55)	2	76.50 (21.50)	2	40.00 (3.00)	2	52.00 (9.00)
	43	2	15.00 (0.00)	2	18.90 (0.60)	2	82.50 (20.50)	2	43.00 (3.00)	2	56.00 (9.00)
	44	2	15.00 (0.00)	2	18.60 (0.60)	1	101.00 (n/a)	1	55.00 (n/a)	1	72.00 (n/a)
	45	2	15.00 (0.00)	2	18.75 (1.45)	1	100.00 (n/a)	1	48.00 (n/a)	1	64.00 (n/a)
	46	2	15.00 (0.00)	2	18.75 (1.25)	1	100.00 (n/a)	1	52.00 (n/a)	1	69.00 (n/a)
	47	2	15.00 (0.00)	2	18.30 (1.30)	1	107.00 (n/a)	1	53.00 (n/a)	1	73.00 (n/a)
	48	2	15.00 (0.00)	2	18.15 (0.95)	1	124.00 (n/a)	1	82.00 (n/a)	1	96.00 (n/a)

Table A2b. Descriptive Statistics for Respiratory Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Respiratory Rate (Breathes/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/NAC (Cont'd)	49	2	15.00 (0.00)	2	18.65 (0.65)	1	104.00 (n/a)	1	68.00 (n/a)	1	82.00 (n/a)
	50	2	15.00 (0.00)	2	18.20 (0.00)	1	102.00 (n/a)	1	52.00 (n/a)	1	69.00 (n/a)
	51	2	15.00 (0.00)	2	18.60 (0.20)	1	113.00 (n/a)	1	62.00 (n/a)	1	81.00 (n/a)
	52	2	15.00 (0.00)	2	18.80 (0.00)	1	109.00 (n/a)	1	64.00 (n/a)	1	79.00 (n/a)
	53	2	15.00 (0.00)	2	19.30 (0.60)	1	104.00 (n/a)	1	55.00 (n/a)	1	73.00 (n/a)
	54	2	15.00 (0.00)	2	18.65 (0.55)	1	93.00 (n/a)	1	49.00 (n/a)	1	62.00 (n/a)
	55	2	15.00 (0.00)	2	18.70 (0.60)	1	105.00 (n/a)	1	57.00 (n/a)	1	76.00 (n/a)
	56	2	15.00 (0.00)	2	19.25 (1.15)	1	84.00 (n/a)	1	40.00 (n/a)	1	54.00 (n/a)
	57	2	15.00 (0.00)	2	19.30 (1.30)	1	112.00 (n/a)	1	66.00 (n/a)	1	84.00 (n/a)
	58	2	15.00 (0.00)	2	18.85 (0.55)	1	92.00 (n/a)	1	44.00 (n/a)	1	59.00 (n/a)
	59	2	15.00 (0.00)	2	18.55 (0.55)	1	97.00 (n/a)	1	49.00 (n/a)	1	64.00 (n/a)
	60	2	15.00 (0.00)	2	19.25 (0.05)	1	109.00 (n/a)	1	70.00 (n/a)	1	82.00 (n/a)
	61	2	15.00 (0.00)	2	19.60 (0.50)	1	117.00 (n/a)	1	71.00 (n/a)	1	88.00 (n/a)
	62	2	15.00 (0.00)	2	17.85 (0.35)	1	105.00 (n/a)	1	53.00 (n/a)	1	71.00 (n/a)
	63	2	15.00 (0.00)	2	17.95 (0.45)	1	110.00 (n/a)	1	57.00 (n/a)	1	75.00 (n/a)
	64	2	15.00 (0.00)	2	18.90 (0.50)	1	106.00 (n/a)	1	56.00 (n/a)	1	74.00 (n/a)
	65	2	15.00 (0.00)	2	19.30 (0.80)	1	103.00 (n/a)	1	56.00 (n/a)	1	72.00 (n/a)
	66	2	15.00 (0.00)	2	18.60 (0.20)	1	106.00 (n/a)	1	56.00 (n/a)	1	74.00 (n/a)
	67	2	15.00 (0.00)	2	18.75 (0.15)	1	108.00 (n/a)	1	59.00 (n/a)	1	77.00 (n/a)
	68	2	15.00 (0.00)	2	19.15 (0.35)	1	112.00 (n/a)	1	71.00 (n/a)	1	85.00 (n/a)
	69	2	15.00 (0.00)	2	19.40 (0.30)	1	99.00 (n/a)	1	51.00 (n/a)	1	67.00 (n/a)
	70	2	15.00 (0.00)	2	19.05 (0.05)	1	106.00 (n/a)	1	59.00 (n/a)	1	75.00 (n/a)
	71	2	15.00 (0.00)	2	15.50 (3.50)	1	101.00 (n/a)	1	51.00 (n/a)	1	67.00 (n/a)
Air/None	0	6	15.00 (0.00)	3	18.93 (3.55)	4	97.50 (7.41)	4	62.25 (6.02)	4	77.25 (4.85)
	1	6	14.83 (0.17)	6	23.03 (1.74)	6	101.25 (7.00)	6	62.00 (1.91)	6	77.83 (3.62)
	2	6	14.67 (0.33)	6	22.40 (1.28)	6	101.00 (5.60)	6	65.67 (5.35)	6	79.50 (4.61)
	3	6	14.67 (0.33)	6	21.28 (0.75)	6	101.83 (5.85)	6	64.17 (4.36)	6	78.17 (3.58)
	4	6	14.67 (0.33)	6	21.02 (1.01)	6	93.33 (6.38)	6	58.00 (2.76)	6	70.50 (2.19)
	5	6	14.67 (0.33)	6	21.48 (1.16)	6	96.17 (5.06)	6	56.17 (3.06)	6	67.50 (3.27)
	6	6	14.67 (0.33)	6	21.22 (1.08)	6	100.33 (10.35)	6	67.50 (8.19)	6	78.33 (8.58)
	7	5	14.60 (0.40)	5	20.72 (1.06)	5	121.80 (6.97)	5	73.00 (6.28)	5	91.40 (6.64)
	8	6	14.67 (0.33)	6	21.15 (1.14)	6	104.00 (5.93)	6	68.67 (7.64)	6	81.67 (6.84)
	9	6	14.67 (0.33)	6	21.03 (1.20)	6	105.33 (9.30)	6	66.50 (8.23)	6	80.33 (8.52)
	10	6	14.67 (0.33)	6	21.08 (0.83)	6	98.50 (7.55)	6	61.50 (6.20)	6	75.17 (7.33)
	11	6	14.67 (0.33)	6	21.27 (0.81)	6	101.33 (8.18)	6	59.50 (7.27)	6	74.50 (7.96)
	12	6	14.67 (0.33)	6	20.88 (0.95)	6	104.17 (7.52)	6	70.33 (6.60)	6	83.17 (6.04)
	13	6	14.67 (0.33)	6	21.28 (1.17)	6	106.83 (7.89)	6	66.83 (7.44)	6	82.17 (7.73)
	14	6	14.67 (0.33)	6	21.88 (0.85)	6	100.00 (4.49)	6	68.50 (4.64)	6	79.50 (3.65)
	15	6	14.67 (0.33)	6	21.72 (0.88)	6	102.67 (5.10)	6	66.33 (7.80)	6	79.50 (6.73)
	16	6	14.67 (0.33)	6	21.13 (0.91)	5	98.60 (8.73)	5	59.00 (3.49)	5	73.60 (4.97)
	17	6	14.67 (0.33)	6	21.05 (1.12)	6	91.50 (10.65)	6	58.17 (5.27)	6	69.17 (7.51)

Table A2b. Descriptive Statistics for Respiratory Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Respiratory Rate (Breathes/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/None (Cont'd)	18	6	14.67 (0.33)	6	21.10 (0.92)	5	99.00 (3.52)	5	64.40 (7.15)	5	77.80 (5.04)
	19	6	14.67 (0.33)	6	21.00 (0.94)	5	102.20 (5.76)	5	66.00 (9.67)	5	79.80 (7.90)
	20	6	14.67 (0.33)	6	20.75 (1.17)	5	103.20 (3.65)	5	57.60 (3.61)	5	74.60 (3.30)
	21	6	14.67 (0.33)	6	20.83 (1.20)	5	106.20 (10.50)	5	64.60 (9.45)	5	79.40 (9.67)
	22	6	14.67 (0.33)	6	20.73 (1.27)	5	103.60 (8.02)	5	59.20 (7.28)	5	76.00 (8.15)
	23	6	14.67 (0.33)	6	20.48 (1.06)	5	104.00 (11.20)	5	60.60 (8.23)	5	76.40 (8.98)
	24	6	14.67 (0.33)	6	20.90 (1.26)	5	102.40 (5.70)	5	59.60 (6.93)	5	75.60 (5.71)
	25	6	14.67 (0.33)	6	20.88 (1.26)	5	97.00 (7.57)	5	54.80 (5.08)	5	70.60 (5.18)
	26	6	14.67 (0.33)	6	20.53 (1.29)	5	100.00 (4.83)	5	57.80 (6.30)	5	73.60 (5.33)
	27	6	14.67 (0.33)	6	20.55 (1.20)	5	98.80 (7.84)	5	57.00 (9.52)	5	71.60 (8.52)
	28	6	14.67 (0.33)	6	21.18 (1.48)	5	101.20 (7.12)	5	64.00 (9.45)	5	77.80 (8.11)
	29	6	14.67 (0.33)	6	20.75 (1.36)	5	104.00 (8.09)	5	64.80 (8.83)	5	79.80 (7.61)
	30	6	14.67 (0.33)	6	19.82 (1.12)	5	99.20 (10.23)	5	54.80 (6.19)	5	71.60 (7.56)
	31	5	15.00 (0.00)	5	19.30 (1.23)	4	98.50 (13.28)	4	60.50 (11.85)	4	74.50 (12.28)
	32	6	14.67 (0.33)	6	20.03 (1.23)	5	109.20 (8.56)	5	72.80 (12.29)	5	85.40 (10.06)
	33	6	14.67 (0.33)	6	19.97 (1.15)	5	105.20 (11.43)	5	63.80 (6.61)	5	78.60 (7.39)
	34	6	14.67 (0.33)	6	20.10 (1.15)	5	107.40 (9.06)	5	64.40 (8.80)	5	79.00 (8.25)
	35	6	14.67 (0.33)	6	20.12 (0.99)	5	99.20 (8.03)	5	56.60 (6.76)	5	71.40 (7.35)
	36	6	14.67 (0.33)	6	19.85 (1.14)	5	108.20 (7.96)	5	65.80 (13.58)	5	80.80 (11.34)
	37	6	14.67 (0.33)	6	19.80 (1.16)	5	97.00 (9.61)	5	56.20 (6.89)	5	70.00 (7.93)
	38	6	14.67 (0.33)	6	19.43 (0.95)	5	94.60 (6.74)	5	54.60 (6.55)	5	69.00 (6.76)
	39	6	14.67 (0.33)	6	19.50 (0.82)	5	110.60 (3.17)	5	64.40 (5.01)	5	81.20 (4.09)
	40	6	14.67 (0.33)	6	19.27 (0.85)	5	109.40 (4.78)	5	64.40 (7.39)	5	78.20 (4.94)
	41	6	14.67 (0.33)	6	19.38 (0.84)	5	99.00 (10.01)	5	60.80 (9.04)	5	74.20 (9.42)
	42	6	14.67 (0.33)	6	19.47 (1.04)	5	101.00 (4.97)	5	60.60 (9.53)	5	74.80 (8.16)
	43	6	14.67 (0.33)	6	19.58 (1.07)	5	91.00 (8.26)	5	47.80 (4.37)	5	62.60 (5.81)
	44	6	14.67 (0.33)	6	19.67 (1.16)	5	96.20 (6.41)	5	55.20 (9.11)	5	68.80 (8.18)
	45	6	14.67 (0.33)	6	19.63 (1.27)	5	91.80 (6.63)	5	52.60 (7.93)	5	65.40 (7.63)
	46	6	14.67 (0.33)	6	19.55 (0.87)	5	96.80 (5.18)	5	57.40 (11.13)	5	70.60 (8.82)
	47	6	14.67 (0.33)	6	19.70 (0.92)	5	96.00 (6.96)	5	50.20 (6.19)	5	66.00 (7.38)
	48	6	14.67 (0.33)	6	19.17 (1.12)	5	98.00 (8.07)	5	61.80 (12.87)	5	74.60 (11.78)
	49	6	14.67 (0.33)	6	19.20 (1.20)	5	102.80 (7.84)	5	65.00 (13.39)	5	77.40 (12.10)
	50	5	15.00 (0.00)	5	19.18 (1.21)	4	103.50 (6.98)	4	62.50 (9.99)	4	77.75 (9.08)
	51	6	14.67 (0.33)	6	19.13 (0.88)	5	100.00 (8.92)	5	55.40 (11.06)	5	70.40 (10.95)
	52	6	14.67 (0.33)	6	18.67 (1.21)	5	104.20 (8.28)	5	62.60 (14.89)	5	76.40 (12.38)
	53	6	14.67 (0.33)	6	18.43 (1.17)	5	106.40 (7.23)	5	64.00 (13.44)	5	77.20 (11.81)
	54	6	14.67 (0.33)	6	18.55 (0.92)	5	102.40 (6.33)	5	58.00 (6.91)	5	73.20 (6.51)
	55	6	14.67 (0.33)	6	18.75 (0.79)	5	97.00 (8.85)	5	53.80 (6.11)	5	69.20 (6.95)
	56	6	14.67 (0.33)	6	18.75 (1.06)	5	99.00 (5.72)	5	62.40 (10.19)	5	75.00 (8.77)
	57	6	14.67 (0.33)	6	18.93 (1.13)	5	98.40 (7.15)	5	57.60 (6.45)	5	72.60 (6.70)
	58	5	15.00 (0.00)	5	18.54 (1.32)	4	100.25 (10.01)	4	58.50 (5.17)	4	74.00 (6.84)

Table A2b. Descriptive Statistics for Respiratory Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Respiratory Rate (Breathes/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Air/None (Cont'd)	59	4	15.00 (0.00)	4	19.53 (0.32)	3	90.00 (9.24)	3	51.00 (1.00)	3	65.33 (2.33)
	60	6	14.67 (0.33)	6	18.20 (0.95)	5	101.20 (8.26)	5	57.60 (2.62)	5	74.00 (3.65)
	61	6	14.67 (0.33)	6	18.25 (1.03)	5	97.20 (8.98)	5	54.20 (5.54)	5	69.20 (6.79)
	62	6	14.67 (0.33)	6	18.28 (0.96)	5	94.80 (6.26)	5	49.80 (2.96)	5	65.40 (3.01)
	63	6	14.67 (0.33)	6	18.62 (0.87)	5	101.40 (2.64)	5	53.80 (2.63)	5	70.60 (2.66)
	64	6	14.67 (0.33)	6	18.67 (1.19)	5	99.40 (5.82)	5	55.80 (4.71)	5	71.80 (4.40)
	65	6	14.67 (0.33)	6	18.67 (1.31)	5	97.80 (6.80)	5	55.40 (3.97)	5	70.60 (4.46)
	66	6	14.67 (0.33)	6	18.48 (1.15)	5	93.20 (5.25)	5	47.80 (1.93)	5	63.80 (1.46)
	67	6	14.67 (0.33)	6	18.78 (1.06)	5	92.60 (7.00)	5	47.40 (2.75)	5	63.20 (4.12)
	68	6	14.67 (0.33)	6	18.38 (1.14)	5	103.40 (3.19)	5	57.20 (7.36)	5	73.20 (5.40)
	69	6	14.67 (0.33)	6	18.27 (1.11)	5	100.80 (1.80)	5	57.20 (7.32)	5	72.20 (5.34)
	70	6	14.67 (0.33)	6	18.42 (0.99)	5	98.60 (3.98)	5	53.60 (4.69)	5	70.40 (3.68)
	71	6	14.67 (0.33)	6	18.63 (0.89)	5	98.00 (4.09)	5	49.80 (2.73)	5	66.20 (3.28)
	72	2	14.00 (1.00)	2	16.67 (2.47)	2	106.83 (8.17)	2	54.50 (11.50)	2	73.17 (11.83)
CG/IBU	0	6	15.00 (0.00)	5	19.12 (1.65)	5	93.40 (4.60)	5	57.40 (7.65)	5	72.80 (6.76)
	1	5	15.00 (0.00)	5	20.52 (1.91)	4	106.75 (4.53)	4	65.00 (5.69)	4	81.50 (5.45)
	2	5	15.00 (0.00)	5	20.18 (0.66)	5	112.40 (7.15)	5	64.40 (7.32)	5	82.00 (7.32)
	3	5	15.00 (0.00)	5	20.86 (0.46)	5	103.00 (1.64)	5	54.20 (2.63)	5	70.80 (2.91)
	4	5	15.00 (0.00)	5	20.86 (0.46)	5	99.00 (4.65)	5	61.80 (3.18)	5	74.80 (2.08)
	5	5	15.00 (0.00)	5	20.46 (0.52)	5	90.80 (7.22)	5	58.60 (6.52)	5	69.60 (5.57)
	6	5	15.00 (0.00)	5	19.86 (0.46)	5	106.80 (6.72)	5	67.40 (6.54)	5	83.20 (5.68)
	7	4	15.00 (0.00)	4	20.30 (0.44)	4	96.50 (8.45)	4	60.00 (11.14)	4	76.25 (9.81)
	8	3	15.00 (0.00)	3	21.00 (0.40)	3	82.67 (6.96)	3	47.67 (6.94)	3	61.33 (5.78)
	9	3	15.00 (0.00)	3	20.03 (0.99)	3	79.67 (5.81)	3	41.67 (3.76)	3	56.67 (4.98)
	10	3	15.00 (0.00)	3	20.53 (0.69)	3	70.67 (9.82)	3	38.67 (4.18)	3	51.00 (5.57)
	11	3	15.00 (0.00)	3	20.73 (0.64)	3	76.67 (11.32)	3	49.00 (4.04)	3	62.00 (4.58)
	12	2	15.00 (0.00)	2	20.35 (0.45)	2	85.50 (2.50)	2	47.50 (4.50)	2	63.50 (2.50)
	13	3	15.00 (0.00)	3	19.07 (0.74)	3	84.67 (12.17)	3	45.00 (8.50)	3	60.33 (9.49)
	14	3	15.00 (0.00)	3	19.45 (0.20)	3	99.33 (12.14)	3	54.33 (9.53)	3	71.33 (9.84)
	15	3	15.00 (0.00)	3	19.75 (0.40)	3	97.33 (10.73)	3	52.67 (6.36)	3	68.67 (7.06)
	16	3	15.00 (0.00)	3	19.73 (0.49)	3	83.67 (11.61)	3	46.33 (6.77)	3	59.33 (7.75)
	17	3	15.00 (0.00)	3	19.17 (0.22)	3	79.67 (10.41)	3	38.67 (6.06)	3	53.33 (8.19)
	18	3	15.00 (0.00)	3	19.20 (0.56)	3	96.33 (18.46)	3	51.00 (12.90)	3	68.67 (15.21)
	19	3	15.00 (0.00)	3	19.67 (0.92)	3	96.67 (6.36)	3	51.67 (4.33)	3	69.33 (4.06)
	20	3	15.00 (0.00)	3	19.60 (0.70)	3	75.00 (12.58)	3	41.00 (6.66)	3	55.00 (8.39)
	21	3	15.00 (0.00)	3	18.57 (0.42)	3	81.00 (7.02)	3	40.00 (5.57)	3	55.67 (5.93)
	22	3	15.00 (0.00)	3	19.00 (0.72)	3	96.00 (0.00)	3	45.67 (3.18)	3	63.33 (2.91)
	23	3	15.00 (0.00)	3	18.70 (1.12)	3	92.33 (3.71)	3	49.67 (1.20)	3	65.67 (1.86)
	24	2	15.00 (0.00)	2	19.00 (1.00)	2	90.00 (13.00)	2	42.50 (6.50)	2	56.50 (6.50)
	25	3	15.00 (0.00)	3	18.73 (0.52)	3	88.33 (5.78)	3	51.33 (8.01)	3	64.33 (7.67)
	26	3	15.00 (0.00)	3	18.67 (0.52)	3	110.33 (9.84)	3	84.33 (20.21)	2	79.00 (10.00)

Table A2b. Descriptive Statistics for Respiratory Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Respiratory Rate (Breathes/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/IBU (Cont'd)	27	3	15.00 (0.00)	3	18.67 (0.39)	3	97.00 (6.00)	3	48.00 (6.66)	3	66.33 (7.17)
	28	2	15.00 (0.00)	2	18.25 (0.85)	2	108.50 (5.50)	2	62.50 (6.50)	2	80.00 (6.00)
	29	2	15.00 (0.00)	2	18.25 (1.15)	2	102.00 (6.00)	2	55.00 (0.00)	2	72.50 (2.50)
	30	2	15.00 (0.00)	2	18.70 (0.40)	2	99.00 (4.00)	2	41.50 (8.50)	2	69.50 (1.50)
	31	2	15.00 (0.00)	2	18.05 (0.05)	2	104.50 (4.50)	2	54.00 (0.00)	2	73.50 (2.50)
	32	2	15.00 (0.00)	2	17.55 (0.45)	2	107.00 (10.00)	2	52.50 (2.50)	2	73.00 (6.00)
	33	2	15.00 (0.00)	2	17.65 (0.35)	2	114.50 (4.50)	2	61.00 (3.00)	2	80.50 (0.50)
	34	2	15.00 (0.00)	2	17.25 (0.75)	2	112.50 (5.50)	2	59.50 (0.50)	2	79.00 (1.00)
	35	2	15.00 (0.00)	2	17.50 (0.50)	2	113.00 (17.00)	2	55.50 (6.50)	2	77.00 (12.00)
	36	2	15.00 (0.00)	2	17.40 (0.60)	2	113.00 (14.00)	2	58.00 (7.00)	2	78.00 (10.00)
	37	2	15.00 (0.00)	2	17.70 (0.30)	2	114.00 (11.00)	2	58.00 (3.00)	2	78.50 (6.50)
	38	2	15.00 (0.00)	2	17.70 (0.20)	2	115.50 (4.50)	2	60.00 (0.00)	2	81.00 (1.00)
	39	2	15.00 (0.00)	2	18.00 (0.70)	2	115.50 (12.50)	2	60.00 (5.00)	2	80.50 (7.50)
	40	2	15.00 (0.00)	2	18.15 (0.95)	2	122.00 (10.00)	2	61.00 (4.00)	2	83.50 (6.50)
	41	2	15.00 (0.00)	2	18.00 (0.60)	2	115.50 (6.50)	2	57.50 (1.50)	2	79.00 (1.00)
	42	2	15.00 (0.00)	2	18.00 (0.60)	2	118.50 (5.50)	2	60.00 (3.00)	2	80.00 (1.00)
	43	2	15.00 (0.00)	2	18.40 (0.90)	2	115.00 (13.00)	2	56.50 (2.50)	2	78.00 (6.00)
	44	2	15.00 (0.00)	2	18.05 (1.35)	2	115.50 (11.50)	2	55.00 (1.00)	2	77.00 (5.00)
	45	2	15.00 (0.00)	2	17.80 (1.20)	2	120.50 (2.50)	2	58.00 (0.00)	2	80.50 (0.50)
	46	2	15.00 (0.00)	2	17.95 (0.55)	2	113.00 (13.00)	2	56.00 (3.00)	2	76.50 (6.50)
	47	2	15.00 (0.00)	2	17.90 (0.60)	2	116.00 (18.00)	2	57.00 (8.00)	2	77.50 (11.50)
	48	2	15.00 (0.00)	2	17.75 (1.25)	2	113.50 (15.50)	2	50.00 (3.00)	2	73.00 (8.00)
	49	2	15.00 (0.00)	2	18.10 (0.70)	2	112.00 (9.00)	2	53.00 (1.00)	2	73.50 (2.50)
	50	2	15.00 (0.00)	2	17.95 (0.75)	2	115.00 (11.00)	2	56.00 (3.00)	2	78.00 (6.00)
	51	2	15.00 (0.00)	2	18.15 (0.25)	2	125.00 (11.00)	2	59.50 (1.50)	2	82.50 (5.50)
	52	2	15.00 (0.00)	2	17.55 (0.65)	2	122.50 (10.50)	2	59.00 (2.00)	2	82.50 (5.50)
	53	2	15.00 (0.00)	2	17.70 (0.60)	2	124.50 (17.50)	2	62.50 (5.50)	2	84.50 (10.50)
	54	2	15.00 (0.00)	2	17.50 (0.90)	2	114.00 (23.00)	2	55.00 (12.00)	2	76.50 (18.50)
	55	2	15.00 (0.00)	2	17.90 (1.00)	2	108.00 (27.00)	2	49.00 (14.00)	2	70.00 (21.00)
	56	2	15.00 (0.00)	2	18.45 (0.95)	2	102.00 (18.00)	2	44.50 (8.50)	2	64.50 (13.50)
	57	2	15.00 (0.00)	2	17.55 (0.25)	2	107.00 (30.00)	2	51.00 (18.00)	2	70.50 (23.50)
	58	2	15.00 (0.00)	2	17.15 (0.55)	2	103.50 (25.50)	2	42.00 (8.00)	2	62.50 (15.50)
	59	2	14.50 (0.50)	2	17.15 (0.85)	2	102.50 (21.50)	2	40.00 (8.00)	2	61.00 (14.00)
	60	2	15.00 (0.00)	2	17.50 (0.70)	2	115.50 (14.50)	2	51.50 (8.50)	2	74.50 (12.50)
	61	2	15.00 (0.00)	2	17.75 (0.65)	2	116.50 (9.50)	2	52.50 (1.50)	2	75.50 (5.50)
	62	2	15.00 (0.00)	2	17.70 (0.70)	2	102.00 (17.00)	2	45.00 (9.00)	2	66.00 (14.00)
	63	2	15.00 (0.00)	2	17.55 (0.55)	2	112.00 (12.00)	2	53.00 (10.00)	2	75.50 (12.50)
	64	2	15.00 (0.00)	2	17.80 (0.60)	2	105.00 (22.00)	2	50.50 (16.50)	2	70.50 (21.50)
	65	2	15.00 (0.00)	2	17.85 (0.45)	2	97.00 (21.00)	2	45.50 (13.50)	2	62.50 (19.50)
	66	2	15.00 (0.00)	2	18.00 (0.20)	2	110.50 (12.50)	2	51.50 (8.50)	2	74.00 (12.00)
	67	2	15.00 (0.00)	2	17.75 (0.25)	2	119.00 (7.00)	2	57.50 (5.50)	2	76.50 (3.50)

Table A2b. Descriptive Statistics for Respiratory Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Respiratory Rate (Breathes/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/IBU (Cont'd)	68	2	15.00 (0.00)	2	17.55 (0.25)	2	117.25 (5.75)	2	56.75 (4.25)	2	79.50 (5.50)
	69	1	15.00 (n/a)	1	17.60 (n/a)	1	110.00 (n/a)	1	54.00 (n/a)	1	77.00 (n/a)
	70	2	15.00 (0.00)	2	17.05 (0.15)	2	102.50 (15.50)	2	44.00 (7.00)	2	65.00 (12.00)
	71	2	14.00 (1.00)	2	17.25 (0.05)	2	102.50 (19.50)	2	45.50 (12.50)	2	66.00 (17.00)
	72	1	15.00 (n/a)	1	17.68 (n/a)	1	94.15 (n/a)	1	43.23 (n/a)	1	60.31 (n/a)
CG/NAC	0	3	15.00 (0.00)	2	17.80 (0.30)	2	106.00 (0.00)	2	62.50 (8.50)	2	80.50 (6.50)
	1	3	15.00 (0.00)	3	22.12 (1.12)	3	102.17 (4.62)	3	59.33 (6.17)	3	75.83 (3.77)
	2	2	15.00 (0.00)	2	22.95 (0.95)	2	103.50 (3.50)	2	49.50 (2.50)	2	69.50 (2.50)
	3	3	15.00 (0.00)	3	24.07 (1.67)	3	102.00 (2.08)	3	51.67 (2.73)	3	69.00 (1.53)
	4	2	15.00 (0.00)	2	23.15 (1.55)	2	107.00 (10.00)	2	64.00 (3.00)	2	85.50 (11.50)
	5	2	15.00 (0.00)	2	23.10 (1.10)	2	110.50 (14.50)	2	74.50 (11.50)	2	90.00 (0.00)
	6	2	15.00 (0.00)	2	22.90 (1.20)	2	124.00 (18.00)	2	66.00 (7.00)	2	88.50 (14.50)
	7	2	15.00 (0.00)	2	22.55 (1.65)	2	119.00 (11.00)	2	80.00 (15.00)	2	96.75 (3.25)
	8	1	15.00 (n/a)	1	20.50 (n/a)	1	120.00 (n/a)	1	72.00 (n/a)	1	90.00 (n/a)
	9	2	15.00 (0.00)	2	22.15 (0.65)	2	118.50 (12.50)	2	63.50 (13.50)	2	88.00 (10.00)
	10	2	15.00 (0.00)	2	21.40 (0.40)	2	125.00 (4.00)	2	72.00 (12.00)	2	94.50 (6.50)
	11	2	15.00 (0.00)	2	22.65 (0.25)	2	121.00 (8.00)	2	66.00 (14.00)	2	87.50 (10.50)
	12	2	15.00 (0.00)	2	22.80 (0.90)	2	120.50 (2.50)	2	66.50 (8.50)	2	89.00 (4.00)
	13	1	15.00 (n/a)	1	21.60 (n/a)	1	112.00 (n/a)	1	66.00 (n/a)	1	84.00 (n/a)
	14	1	15.00 (n/a)	1	22.50 (n/a)	1	122.00 (n/a)	1	73.00 (n/a)	1	92.00 (n/a)
	15	1	15.00 (n/a)	1	22.30 (n/a)	1	115.00 (n/a)	1	65.00 (n/a)	1	85.00 (n/a)
	16	1	15.00 (n/a)	1	21.00 (n/a)	1	117.00 (n/a)	1	68.00 (n/a)	1	86.00 (n/a)
	17	1	15.00 (n/a)	1	21.10 (n/a)	1	114.00 (n/a)	1	63.00 (n/a)	1	82.00 (n/a)
	18	1	15.00 (n/a)	1	22.80 (n/a)	1	121.00 (n/a)	1	68.00 (n/a)	1	88.00 (n/a)
	19	1	15.00 (n/a)	1	24.10 (n/a)	1	117.00 (n/a)	1	64.00 (n/a)	1	80.00 (n/a)
	20	1	15.00 (n/a)	1	23.00 (n/a)	1	122.00 (n/a)	1	68.00 (n/a)	1	89.00 (n/a)
	21	1	15.00 (n/a)	1	23.30 (n/a)	1	112.00 (n/a)	1	60.00 (n/a)	1	79.00 (n/a)
	22	1	15.00 (n/a)	1	23.00 (n/a)	1	126.00 (n/a)	1	70.00 (n/a)	1	91.00 (n/a)
	23	1	15.00 (n/a)	1	23.20 (n/a)	1	121.00 (n/a)	1	68.00 (n/a)	1	89.00 (n/a)
	24	1	15.00 (n/a)	1	22.90 (n/a)	1	120.00 (n/a)	1	68.00 (n/a)	1	88.00 (n/a)
	25	1	15.00 (n/a)	1	23.10 (n/a)	1	107.00 (n/a)	1	57.00 (n/a)	1	76.50 (n/a)
	27	1	15.00 (n/a)	1	22.50 (n/a)	1	109.00 (n/a)	1	83.00 (n/a)	1	93.00 (n/a)
	28	1	15.00 (n/a)	1	22.20 (n/a)	1	103.00 (n/a)	1	65.00 (n/a)	1	81.00 (n/a)
	29	1	15.00 (n/a)	1	22.50 (n/a)	1	104.00 (n/a)	1	74.00 (n/a)	1	87.00 (n/a)
	30	1	15.00 (n/a)	1	22.60 (n/a)	1	123.00 (n/a)	1	66.00 (n/a)	1	89.00 (n/a)
	31	1	15.00 (n/a)	1	22.20 (n/a)	1	104.00 (n/a)	1	76.00 (n/a)	1	90.00 (n/a)
	32	1	15.00 (n/a)	1	22.20 (n/a)	1	96.00 (n/a)	1	70.50 (n/a)	1	81.00 (n/a)
	33	1	15.00 (n/a)	1	22.10 (n/a)	1	102.00 (n/a)	1	60.00 (n/a)	1	78.00 (n/a)
	34	1	15.00 (n/a)	1	21.80 (n/a)	1	118.00 (n/a)	1	90.00 (n/a)	1	101.00 (n/a)

Table A2b. Descriptive Statistics for Respiratory Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Respiratory Rate (Breathes/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/NAC (Cont'd)	35	1	15.00 (n/a)	1	21.70 (n/a)	1	110.00 (n/a)	1	81.00 (n/a)	1	92.00 (n/a)
	36	1	15.00 (n/a)	1	21.30 (n/a)	1	110.00 (n/a)	1	60.00 (n/a)	1	79.00 (n/a)
	37	1	15.00 (n/a)	1	21.10 (n/a)	1	107.00 (n/a)	1	55.00 (n/a)	1	75.00 (n/a)
	38	1	15.00 (n/a)	1	21.00 (n/a)	1	112.00 (n/a)	1	62.00 (n/a)	1	82.00 (n/a)
	39	1	15.00 (n/a)	1	21.10 (n/a)	1	114.00 (n/a)	1	61.00 (n/a)	1	81.00 (n/a)
	40	1	15.00 (n/a)	1	21.20 (n/a)	1	113.00 (n/a)	1	60.00 (n/a)	1	80.00 (n/a)
	41	1	15.00 (n/a)	1	21.50 (n/a)	1	115.00 (n/a)	1	63.00 (n/a)	1	83.00 (n/a)
	42	1	15.00 (n/a)	1	21.50 (n/a)	1	126.00 (n/a)	1	66.00 (n/a)	1	90.00 (n/a)
	43	1	15.00 (n/a)	1	21.50 (n/a)	1	117.00 (n/a)	1	63.00 (n/a)	1	84.00 (n/a)
	44	1	15.00 (n/a)	1	21.50 (n/a)	1	113.00 (n/a)	1	59.00 (n/a)	1	78.00 (n/a)
	45	1	15.00 (n/a)	1	22.00 (n/a)	1	116.00 (n/a)	1	52.00 (n/a)	1	82.00 (n/a)
	46	1	15.00 (n/a)	1	21.80 (n/a)	1	113.00 (n/a)	1	61.00 (n/a)	1	81.00 (n/a)
	47	1	15.00 (n/a)	1	22.30 (n/a)	1	111.00 (n/a)	1	61.00 (n/a)	1	81.00 (n/a)
	48	1	15.00 (n/a)	1	22.20 (n/a)	1	105.00 (n/a)	1	56.00 (n/a)	1	75.00 (n/a)
	49	1	15.00 (n/a)	1	22.30 (n/a)	1	113.00 (n/a)	1	61.00 (n/a)	1	81.00 (n/a)
	50	1	15.00 (n/a)	1	22.00 (n/a)	1	113.00 (n/a)	1	62.00 (n/a)	1	82.00 (n/a)
	51	1	15.00 (n/a)	1	21.20 (n/a)	1	111.00 (n/a)	1	61.00 (n/a)	1	80.00 (n/a)
	52	1	15.00 (n/a)	1	21.20 (n/a)	1	108.00 (n/a)	1	66.00 (n/a)	1	83.00 (n/a)
	53	1	15.00 (n/a)	1	21.10 (n/a)	1	111.00 (n/a)	1	59.00 (n/a)	1	78.00 (n/a)
	54	1	15.00 (n/a)	1	21.20 (n/a)	1	108.00 (n/a)	1	56.00 (n/a)	1	75.00 (n/a)
	55	1	15.00 (n/a)	1	22.80 (n/a)	1	103.00 (n/a)	1	75.00 (n/a)	1	85.00 (n/a)
	56	1	15.00 (n/a)	1	22.70 (n/a)	1	105.00 (n/a)	1	58.00 (n/a)	1	76.00 (n/a)
	57	1	15.00 (n/a)	1	22.20 (n/a)	1	103.00 (n/a)	1	56.00 (n/a)	1	74.00 (n/a)
	58	1	15.00 (n/a)	1	22.50 (n/a)	1	97.00 (n/a)	1	52.00 (n/a)	1	69.00 (n/a)
	59	1	15.00 (n/a)	1	21.70 (n/a)	1	107.00 (n/a)	1	60.00 (n/a)	1	78.00 (n/a)
	60	1	15.00 (n/a)	1	21.40 (n/a)	1	107.00 (n/a)	1	57.00 (n/a)	1	76.00 (n/a)
	61	1	15.00 (n/a)	1	20.40 (n/a)	1	109.00 (n/a)	1	58.00 (n/a)	1	78.00 (n/a)
	62	1	15.00 (n/a)	1	20.90 (n/a)	1	105.00 (n/a)	1	55.00 (n/a)	1	75.00 (n/a)
	63	1	15.00 (n/a)	1	20.90 (n/a)	1	101.00 (n/a)	1	50.00 (n/a)	1	69.00 (n/a)
	64	1	15.00 (n/a)	1	20.60 (n/a)	1	111.00 (n/a)	1	58.00 (n/a)	1	77.00 (n/a)
	65	1	15.00 (n/a)	1	20.40 (n/a)	1	104.00 (n/a)	1	52.00 (n/a)	1	70.00 (n/a)
	66	1	15.00 (n/a)	1	20.40 (n/a)	1	109.00 (n/a)	1	57.00 (n/a)	1	76.00 (n/a)
	67	1	15.00 (n/a)	1	21.40 (n/a)	1	105.00 (n/a)	1	54.00 (n/a)	1	73.00 (n/a)
	68	1	15.00 (n/a)	1	20.40 (n/a)	1	108.00 (n/a)	1	56.00 (n/a)	1	76.00 (n/a)
	69	1	15.00 (n/a)	1	20.40 (n/a)	1	108.00 (n/a)	1	54.00 (n/a)	1	74.00 (n/a)
	70	1	15.00 (n/a)	1	20.50 (n/a)	1	101.00 (n/a)	1	49.00 (n/a)	1	67.00 (n/a)
	71	1	15.00 (n/a)	1	20.60 (n/a)	1	109.00 (n/a)	1	56.00 (n/a)	1	75.00 (n/a)
	72	1	15.00 (n/a)	1	19.90 (n/a)	1	109.00 (n/a)	1	56.00 (n/a)	1	76.00 (n/a)

Table A2b. Descriptive Statistics for Respiratory Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Exposure/Treatment Groups and Study Timecourse (continued).

Group	Study Time-course	Respiratory Rate (Breathes/Minute)		Impedance Cardiograph (Ohms)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Mean Blood Pressure (mm Hg)	
		N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
CG/None	0	5	15.00 (0.00)	5	19.00 (1.12)	4	101.25 (5.53)	4	62.25 (3.17)	4	78.50 (3.77)
	1	6	15.00 (0.00)	6	21.43 (1.50)	6	107.17 (2.47)	6	65.17 (3.48)	6	82.00 (2.79)
	2	6	15.00 (0.00)	6	20.37 (1.29)	6	110.50 (4.07)	6	65.50 (3.27)	6	82.33 (2.85)
	3	6	15.00 (0.00)	6	21.28 (1.26)	6	105.17 (4.59)	6	64.33 (3.84)	6	79.50 (3.49)
	4	6	15.00 (0.00)	6	20.73 (1.30)	6	102.83 (5.57)	6	57.67 (4.00)	6	74.33 (4.37)
	5	6	15.00 (0.00)	6	20.73 (1.09)	6	103.67 (11.02)	6	58.50 (7.42)	6	74.50 (8.53)
	6	6	15.00 (0.00)	6	21.02 (0.99)	6	104.83 (12.42)	6	68.17 (7.94)	6	82.33 (9.15)
	7	6	15.00 (0.00)	6	20.82 (1.01)	6	96.33 (8.93)	6	57.83 (6.25)	6	71.83 (7.60)
	8	5	15.00 (0.00)	5	21.86 (0.67)	5	91.40 (6.71)	5	61.60 (8.17)	5	67.80 (8.33)
	9	4	15.00 (0.00)	4	21.90 (0.57)	4	91.00 (7.36)	4	70.00 (11.70)	4	78.00 (8.77)
	10	5	15.00 (0.00)	5	22.25 (0.83)	4	91.25 (9.75)	4	51.50 (9.82)	4	65.00 (10.22)
	11	5	15.00 (0.00)	5	21.99 (0.80)	5	82.60 (12.63)	5	44.60 (12.58)	5	63.20 (14.86)
	12	5	15.00 (0.00)	5	21.80 (0.70)	5	89.60 (11.95)	5	57.60 (13.46)	5	68.00 (12.87)
	13	4	15.00 (0.00)	4	22.30 (0.68)	3	91.67 (3.48)	3	52.33 (7.97)	3	66.33 (5.33)
	14	3	15.00 (0.00)	3	23.20 (0.46)	3	108.67 (13.86)	3	66.00 (6.66)	3	82.33 (5.93)
	15	3	15.00 (0.00)	3	22.87 (0.07)	3	114.67 (14.25)	3	69.67 (8.25)	3	86.33 (7.31)
	16	3	15.00 (0.00)	3	22.33 (0.59)	3	94.33 (6.57)	3	60.00 (4.04)	3	75.00 (3.21)
	17	3	15.00 (0.00)	3	21.95 (0.75)	3	79.33 (13.67)	3	55.00 (8.14)	3	67.67 (10.48)
	18	3	15.00 (0.00)	3	22.23 (0.90)	2	113.00 (17.00)	2	58.50 (4.50)	2	79.50 (6.50)
	19	3	15.00 (0.00)	3	22.40 (1.04)	2	97.00 (10.00)	2	63.50 (19.50)	2	76.50 (15.50)
	20	2	15.00 (0.00)	2	22.65 (0.85)	2	100.00 (10.00)	2	65.50 (16.50)	2	81.50 (16.50)
	21	2	15.00 (0.00)	2	22.35 (0.85)	2	98.50 (0.50)	2	56.50 (0.50)	2	70.50 (3.50)
	22	2	14.50 (0.50)	2	23.45 (1.95)	1	162.00 (n/a)	1	93.00 (n/a)	1	118.00 (n/a)
	23	1	14.00 (n/a)	1	24.90 (n/a)	1	124.00 (n/a)	1	88.00 (n/a)	1	113.00 (n/a)
	24	1	15.00 (n/a)	1	24.30 (n/a)	1	165.00 (n/a)	1	91.00 (n/a)	1	115.00 (n/a)
	25	1	15.00 (n/a)	1	22.70 (n/a)	1	130.00 (n/a)	1	67.00 (n/a)	1	91.00 (n/a)
	26	1	15.00 (n/a)	1	23.10 (n/a)	1	142.00 (n/a)	1	82.00 (n/a)	1	104.00 (n/a)
	27	1	15.00 (n/a)	1	22.80 (n/a)	1	136.00 (n/a)	1	77.00 (n/a)	1	99.00 (n/a)
	28	1	15.00 (n/a)	1	24.50 (n/a)	1	112.00 (n/a)	1	56.00 (n/a)	1	76.00 (n/a)
	29	1	15.00 (n/a)	1	24.10 (n/a)	1	144.00 (n/a)	1	83.00 (n/a)	1	102.00 (n/a)
	30	1	15.00 (n/a)	1	23.20 (n/a)	1	150.00 (n/a)	1	82.00 (n/a)	1	105.00 (n/a)
	31	1	15.00 (n/a)	1	23.30 (n/a)	1	147.00 (n/a)	1	83.00 (n/a)	1	104.00 (n/a)
	32	1	15.00 (n/a)	1	23.00 (n/a)	1	139.00 (n/a)	1	76.00 (n/a)	1	97.00 (n/a)
	33	1	15.00 (n/a)	1	23.10 (n/a)	1	133.00 (n/a)	1	75.00 (n/a)	1	98.00 (n/a)
	34	1	15.00 (n/a)	1	23.80 (n/a)	1	119.00 (n/a)	1	65.00 (n/a)	1	85.00 (n/a)
	35	1	15.00 (n/a)	1	24.30 (n/a)	1	124.00 (n/a)	1	77.00 (n/a)	1	95.00 (n/a)
	36	1	15.00 (n/a)	1	24.00 (n/a)	1	130.00 (n/a)	1	80.00 (n/a)	1	98.00 (n/a)
	37	1	15.00 (n/a)	1	23.70 (n/a)	1	108.00 (n/a)	1	57.00 (n/a)	1	75.00 (n/a)
	38	1	15.00 (n/a)	1	24.80 (n/a)	1	125.00 (n/a)	1	75.00 (n/a)	1	94.00 (n/a)
	39	1	15.00 (n/a)	1	24.60 (n/a)	1	82.00 (n/a)	1	58.00 (n/a)	1	69.00 (n/a)
	41	1	15.00 (n/a)	1	24.35 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)

Table A2b. Descriptive Statistics for Respiratory Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Exposure/Treatment Groups and Study Timecourse (continued).

CG/None (Cont'd)	42	1	15.00 (n/a)	1	25.20 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	43	1	15.00 (n/a)	1	25.10 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	44	1	15.00 (n/a)	1	24.80 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	45	1	15.00 (n/a)	1	24.60 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	46	1	15.00 (n/a)	1	25.00 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	47	1	15.00 (n/a)	1	24.50 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	48	1	15.00 (n/a)	1	24.00 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	49	1	15.00 (n/a)	1	23.40 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	50	1	15.00 (n/a)	1	24.60 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	51	1	15.00 (n/a)	1	24.70 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	52	1	15.00 (n/a)	1	24.90 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	53	1	15.00 (n/a)	1	23.80 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	54	1	15.00 (n/a)	1	23.30 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	55	1	15.00 (n/a)	1	23.20 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	56	1	15.00 (n/a)	1	23.50 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	57	1	15.00 (n/a)	1	22.50 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	58	1	15.00 (n/a)	1	23.40 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	59	1	15.00 (n/a)	1	23.60 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	60	1	15.00 (n/a)	1	24.80 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	61	1	15.00 (n/a)	1	24.70 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	62	1	15.00 (n/a)	1	25.00 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	63	1	15.00 (n/a)	1	25.10 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	64	1	15.00 (n/a)	1	24.20 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	65	1	15.00 (n/a)	1	24.00 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	66	1	15.00 (n/a)	1	26.20 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	67	1	15.00 (n/a)	1	24.80 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	68	1	15.00 (n/a)	1	24.00 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	69	1	15.00 (n/a)	1	23.60 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	70	1	15.00 (n/a)	1	24.40 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
	71	1	15.00 (n/a)	1	24.00 (n/a)	0	n/a (n/a)	0	n/a (n/a)	0	n/a (n/a)
CG/PEEP	0	4	15.00 (0.00)	3	20.00 (1.68)	4	87.50 (5.81)	4	63.00 (6.06)	4	71.50 (4.70)
	1	4	15.00 (0.00)	4	20.20 (1.85)	4	82.88 (6.21)	4	52.50 (5.06)	4	63.75 (5.92)
	2	4	15.00 (0.00)	4	20.34 (1.59)	4	86.25 (6.71)	4	55.75 (6.49)	4	66.75 (6.56)
	3	3	15.00 (0.00)	4	21.30 (0.60)	3	74.00 (6.81)	3	46.67 (5.36)	3	58.33 (5.17)
	4	3	15.00 (0.00)	3	20.07 (0.30)	3	80.00 (8.02)	3	41.00 (8.39)	3	52.67 (5.24)
	5	3	15.00 (0.00)	3	19.63 (0.32)	3	70.00 (5.03)	3	45.33 (3.53)	3	55.67 (2.91)
	6	2	15.00 (0.00)	2	20.45 (0.25)	2	77.00 (8.00)	2	46.00 (3.00)	2	59.00 (6.00)
	7	2	15.00 (0.00)	2	20.00 (0.50)	2	78.50 (6.50)	2	49.50 (5.50)	2	62.50 (3.50)
	8	2	15.00 (0.00)	2	19.65 (0.65)	2	65.50 (0.50)	2	49.00 (9.00)	2	57.50 (5.50)
	9	2	15.00 (0.00)	2	19.50 (0.40)	2	67.50 (2.50)	2	44.50 (4.50)	2	55.00 (1.00)
	10	2	15.00 (0.00)	2	20.65 (1.05)	2	81.00 (0.00)	2	47.50 (1.50)	2	62.50 (0.50)

Table A2b. Descriptive Statistics for Respiratory Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Exposure/Treatment Groups and Study Timecourse (continued).

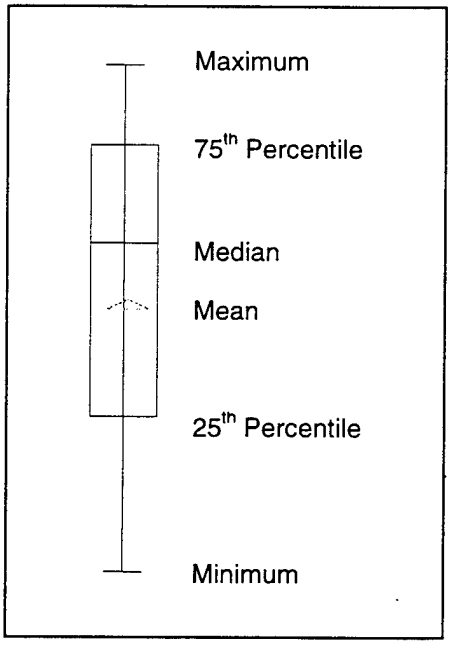
CG/PEEP (Cont'd)	11	2	15.00 (0.00)	2	20.50 (0.40)	2	74.50 (0.50)	2	53.00 (8.00)	2	63.00 (4.00)
	12	2	15.00 (0.00)	2	20.50 (0.30)	2	89.50 (25.50)	2	61.00 (23.00)	2	71.50 (21.50)
	13	2	15.00 (0.00)	2	20.10 (0.10)	2	58.50 (12.50)	2	39.00 (12.00)	2	48.50 (12.50)
	14	2	15.00 (0.00)	2	21.10 (0.60)	2	56.00 (25.00)	2	34.00 (15.00)	2	43.50 (19.50)
	15	1	15.00 (n/a)	1	21.40 (n/a)	1	89.00 (n/a)	1	58.00 (n/a)	1	73.00 (n/a)
	16	1	15.00 (n/a)	1	21.20 (n/a)	1	84.00 (n/a)	1	60.00 (n/a)	1	70.00 (n/a)
	17	1	15.00 (n/a)	1	20.80 (n/a)	1	74.00 (n/a)	1	48.00 (n/a)	1	58.00 (n/a)
	18	1	15.00 (n/a)	1	21.00 (n/a)	1	78.00 (n/a)	1	48.00 (n/a)	1	60.00 (n/a)
	19	1	15.00 (n/a)	1	20.50 (n/a)	1	91.00 (n/a)	1	57.00 (n/a)	1	70.00 (n/a)
	20	1	15.00 (n/a)	1	21.20 (n/a)	1	86.00 (n/a)	1	58.00 (n/a)	1	67.00 (n/a)
	21	1	15.00 (n/a)	1	20.10 (n/a)	1	63.00 (n/a)	1	41.00 (n/a)	1	49.00 (n/a)
	22	1	15.00 (n/a)	1	20.70 (n/a)	1	123.00 (n/a)	1	119.00 (n/a)	1	120.00 (n/a)
	23	1	15.00 (n/a)	1	21.00 (n/a)	1	81.00 (n/a)	1	72.00 (n/a)	1	76.00 (n/a)
	24	1	15.00 (n/a)	1	19.50 (n/a)	1	57.00 (n/a)	1	49.00 (n/a)	1	55.00 (n/a)
	25	1	15.00 (n/a)	1	19.50 (n/a)	1	45.00 (n/a)	1	29.00 (n/a)	1	33.00 (n/a)
	26	1	15.00 (n/a)	1	20.40 (n/a)	1	40.00 (n/a)	1	28.00 (n/a)	1	32.00 (n/a)
	27	1	15.00 (n/a)	1	20.20 (n/a)	1	60.00 (n/a)	1	38.00 (n/a)	1	46.00 (n/a)
	28	1	15.00 (n/a)	1	18.40 (n/a)	1	80.00 (n/a)	1	55.00 (n/a)	1	65.00 (n/a)
	29	1	15.00 (n/a)	1	18.50 (n/a)	1	89.00 (n/a)	1	65.00 (n/a)	1	74.00 (n/a)
	30	1	15.00 (n/a)	1	18.70 (n/a)	1	90.00 (n/a)	1	60.00 (n/a)	1	72.00 (n/a)
	31	1	15.00 (n/a)	1	18.60 (n/a)	1	82.00 (n/a)	1	54.00 (n/a)	1	66.00 (n/a)
	32	1	15.00 (n/a)	1	18.20 (n/a)	1	80.00 (n/a)	1	67.00 (n/a)	1	72.00 (n/a)
	33	1	15.00 (n/a)	1	18.20 (n/a)	1	89.00 (n/a)	1	69.00 (n/a)	1	77.00 (n/a)
	34	1	15.00 (n/a)	1	18.00 (n/a)	1	102.00 (n/a)	1	63.00 (n/a)	1	78.00 (n/a)
	35	1	15.00 (n/a)	1	18.20 (n/a)	1	102.00 (n/a)	1	61.00 (n/a)	1	77.00 (n/a)
	36	1	15.00 (n/a)	1	17.80 (n/a)	1	102.00 (n/a)	1	64.00 (n/a)	1	79.00 (n/a)
	37	1	15.00 (n/a)	1	17.70 (n/a)	1	94.00 (n/a)	1	59.00 (n/a)	1	73.00 (n/a)
	38	1	15.00 (n/a)	1	19.50 (n/a)	1	110.00 (n/a)	1	67.00 (n/a)	1	83.00 (n/a)
	39	1	15.00 (n/a)	1	19.50 (n/a)	1	96.00 (n/a)	1	56.00 (n/a)	1	71.00 (n/a)
	40	1	15.00 (n/a)	1	18.20 (n/a)	1	99.00 (n/a)	1	63.00 (n/a)	1	77.00 (n/a)
	41	1	15.00 (n/a)	1	18.00 (n/a)	1	116.00 (n/a)	1	75.00 (n/a)	1	90.00 (n/a)
	42	1	15.00 (n/a)	1	19.00 (n/a)	1	101.00 (n/a)	1	59.00 (n/a)	1	75.00 (n/a)
	43	1	15.00 (n/a)	1	18.90 (n/a)	1	100.00 (n/a)	1	57.00 (n/a)	1	73.00 (n/a)
	44	1	15.00 (n/a)	1	17.80 (n/a)	1	90.00 (n/a)	1	67.00 (n/a)	1	78.00 (n/a)
	45	1	15.00 (n/a)	1	17.70 (n/a)	1	85.00 (n/a)	1	46.00 (n/a)	1	61.00 (n/a)
	46	1	15.00 (n/a)	1	18.20 (n/a)	1	99.00 (n/a)	1	57.00 (n/a)	1	73.00 (n/a)
	47	1	15.00 (n/a)	1	18.50 (n/a)	1	104.00 (n/a)	1	60.00 (n/a)	1	77.00 (n/a)
	48	1	15.00 (n/a)	1	17.50 (n/a)	1	88.00 (n/a)	1	69.00 (n/a)	1	77.00 (n/a)
	49	1	15.00 (n/a)	1	17.50 (n/a)	1	70.00 (n/a)	1	61.00 (n/a)	1	63.00 (n/a)
	50	1	15.00 (n/a)	1	18.30 (n/a)	1	110.00 (n/a)	1	69.00 (n/a)	1	85.00 (n/a)
	51	1	15.00 (n/a)	1	18.80 (n/a)	1	101.00 (n/a)	1	58.00 (n/a)	1	76.00 (n/a)

Table A2b. Descriptive Statistics for Respiratory Rate, Impedance Cardiograph, Systolic Blood Pressure, Diastolic Blood Pressure, and Mean Blood Pressure by Exposure/Treatment Groups and Study Timecourse (continued).

CG/PEEP (Cont'd)	52	1	15.00 (n/a)	1	17.50 (n/a)	1	89.00 (n/a)	1	76.00 (n/a)	1	82.00 (n/a)
	53	1	15.00 (n/a)	1	17.00 (n/a)	1	75.00 (n/a)	1	46.00 (n/a)	1	56.00 (n/a)
	54	1	15.00 (n/a)	1	18.80 (n/a)	1	99.00 (n/a)	1	59.00 (n/a)	1	74.00 (n/a)
	55	1	15.00 (n/a)	1	18.70 (n/a)	1	103.00 (n/a)	1	59.00 (n/a)	1	76.00 (n/a)
	56	1	15.00 (n/a)	1	17.40 (n/a)	1	86.00 (n/a)	1	56.00 (n/a)	1	67.00 (n/a)
	57	1	15.00 (n/a)	1	17.30 (n/a)	1	90.00 (n/a)	1	56.00 (n/a)	1	70.00 (n/a)
	58	1	15.00 (n/a)	1	17.30 (n/a)	1	95.00 (n/a)	1	49.00 (n/a)	1	65.00 (n/a)
	59	1	15.00 (n/a)	1	17.20 (n/a)	1	102.00 (n/a)	1	58.00 (n/a)	1	74.00 (n/a)
	60	1	15.00 (n/a)	1	17.40 (n/a)	1	95.00 (n/a)	1	63.00 (n/a)	1	75.00 (n/a)
	61	1	15.00 (n/a)	1	17.30 (n/a)	1	95.00 (n/a)	1	64.00 (n/a)	1	76.00 (n/a)
	62	1	15.00 (n/a)	1	18.50 (n/a)	1	101.00 (n/a)	1	64.00 (n/a)	1	78.00 (n/a)
	63	1	15.00 (n/a)	1	18.50 (n/a)	1	103.00 (n/a)	1	60.00 (n/a)	1	75.00 (n/a)
	64	1	15.00 (n/a)	1	16.50 (n/a)	1	90.00 (n/a)	1	59.00 (n/a)	1	71.00 (n/a)
	65	1	15.00 (n/a)	1	16.50 (n/a)	1	93.00 (n/a)	1	60.00 (n/a)	1	73.00 (n/a)
	66	1	15.00 (n/a)	1	17.60 (n/a)	1	100.00 (n/a)	1	61.00 (n/a)	1	77.00 (n/a)
	67	1	15.00 (n/a)	1	17.70 (n/a)	1	98.00 (n/a)	1	61.00 (n/a)	1	76.00 (n/a)
	68	1	15.00 (n/a)	1	16.90 (n/a)	1	114.00 (n/a)	1	89.00 (n/a)	1	98.00 (n/a)
	69	1	15.00 (n/a)	1	17.00 (n/a)	1	84.00 (n/a)	1	57.00 (n/a)	1	71.00 (n/a)
	70	1	15.00 (n/a)	1	17.10 (n/a)	1	99.00 (n/a)	1	59.00 (n/a)	1	74.00 (n/a)
	71	1	15.00 (n/a)	1	18.50 (n/a)	1	99.00 (n/a)	1	60.00 (n/a)	1	76.00 (n/a)

APPENDIX B: BOXPLOTS

Key



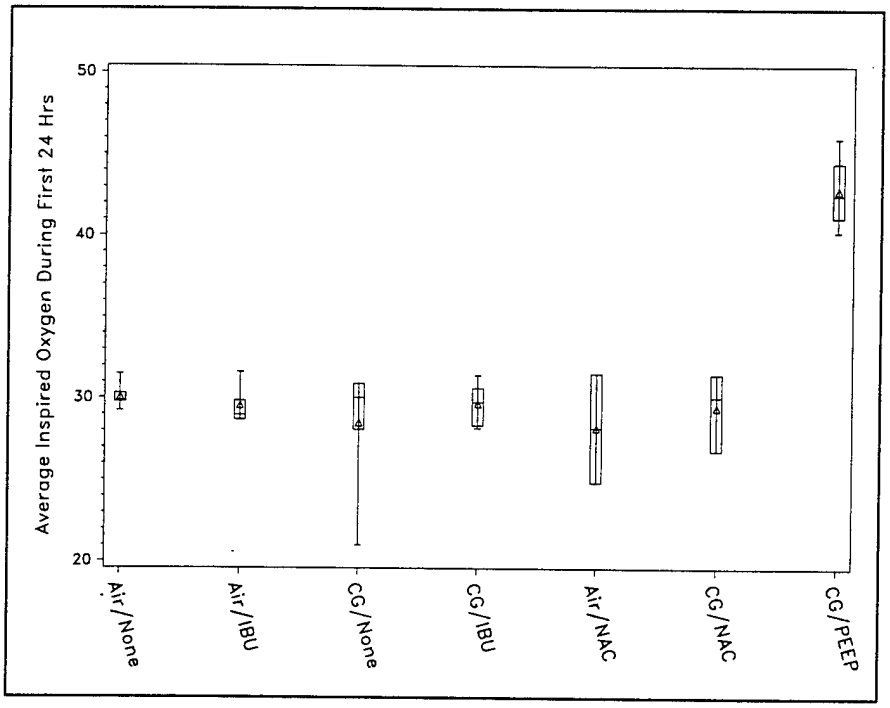


Figure B-1. **Boxplots of Average Inspired Oxygen (%) During First 24 Hours for Seven Exposure/Treatment Groups.**

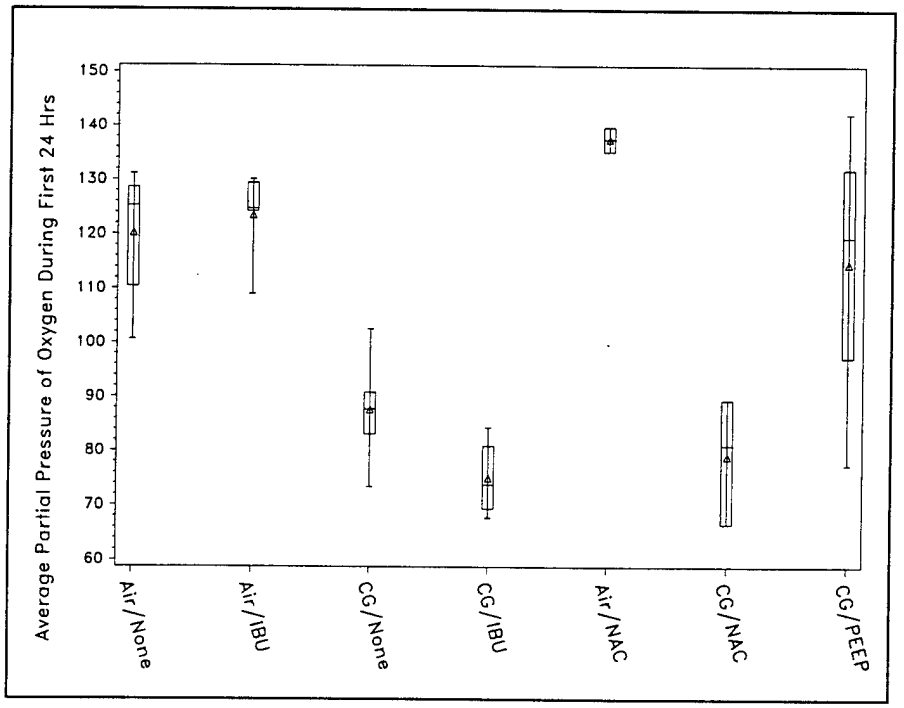


Figure B-2. **Boxplots of Average Arterial Partial Pressure of Oxygen (mm Hg) During First 24 Hours for Seven Exposure/Treatment Groups.**

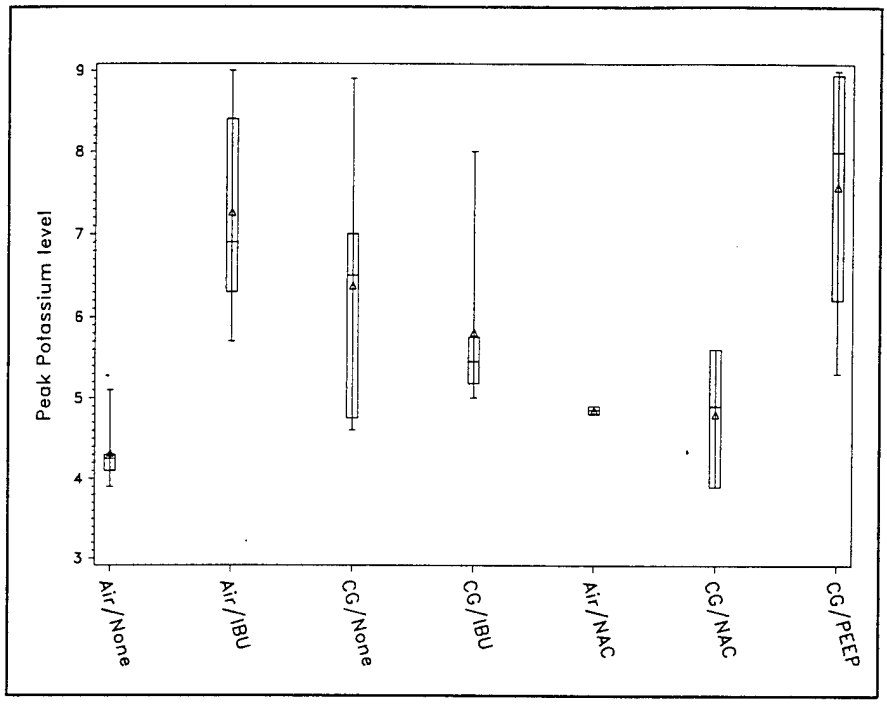


Figure B-3. Boxplots of Peak Potassium Levels (mmol/L) for Seven Exposure/Treatment Groups.

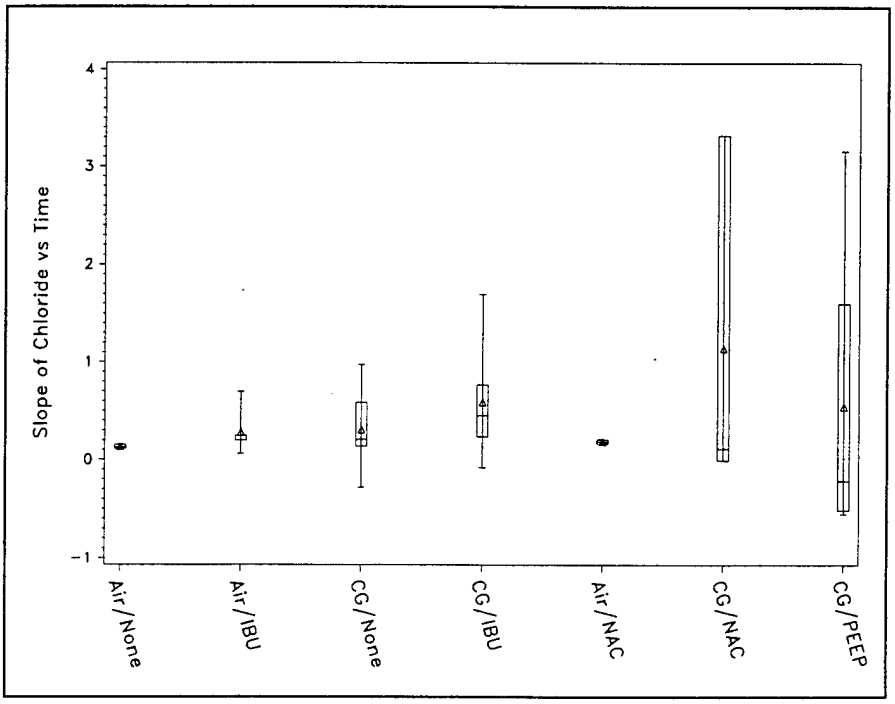


Figure B-4. Boxplots of Slope of Chloride versus Time for Seven Exposure/Treatment Groups.

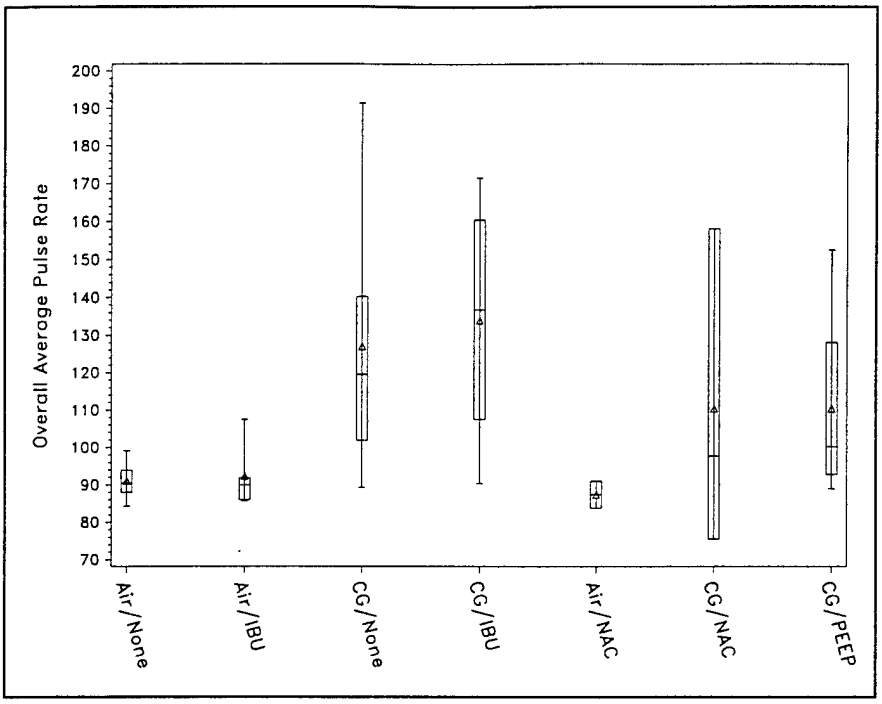


Figure B-5. **Boxplots of Overall Average Pulse Rate (beats/minute) for Seven Exposure/ Treatment Groups.**

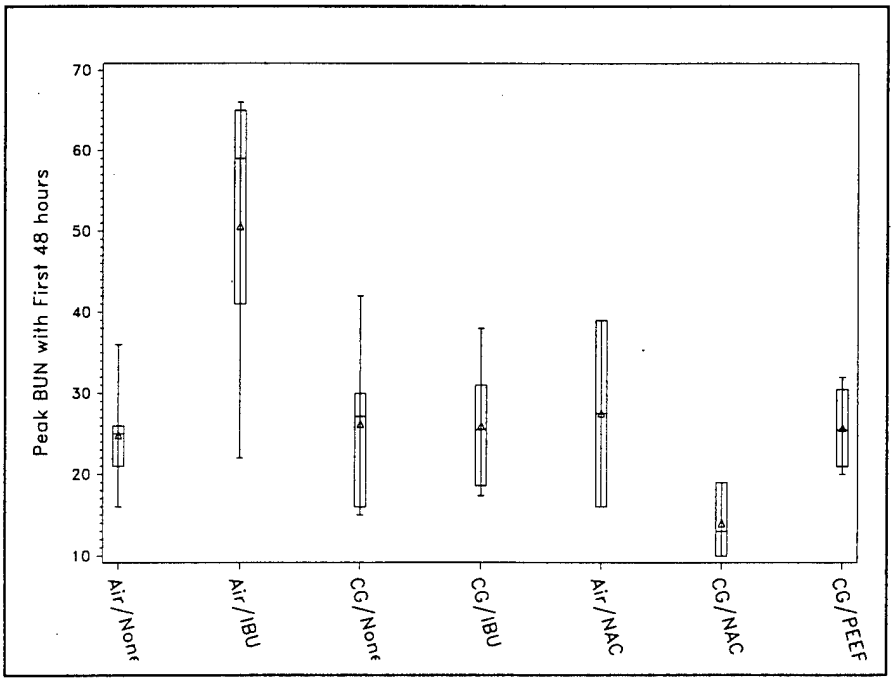


Figure B-6. **Boxplots of Peak Blood Urea Nitrogen (mg/dL) During First 48 Hours for Seven Exposure/Treatment Groups.**

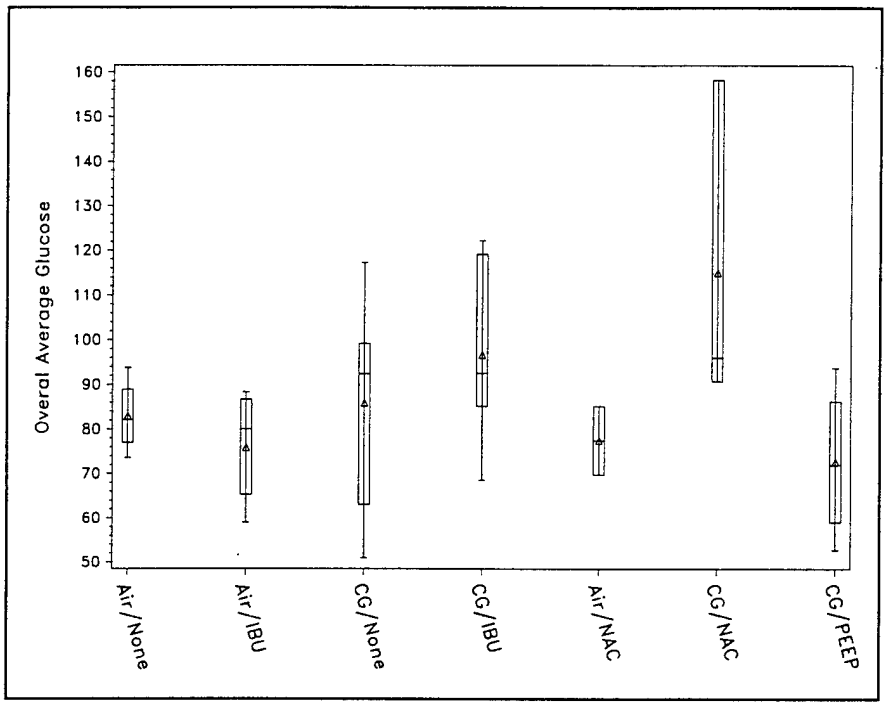


Figure B-7. Boxplots of Average Glucose Levels (mg/dL) During First 24 Hours for Seven Exposure/Treatment Groups.

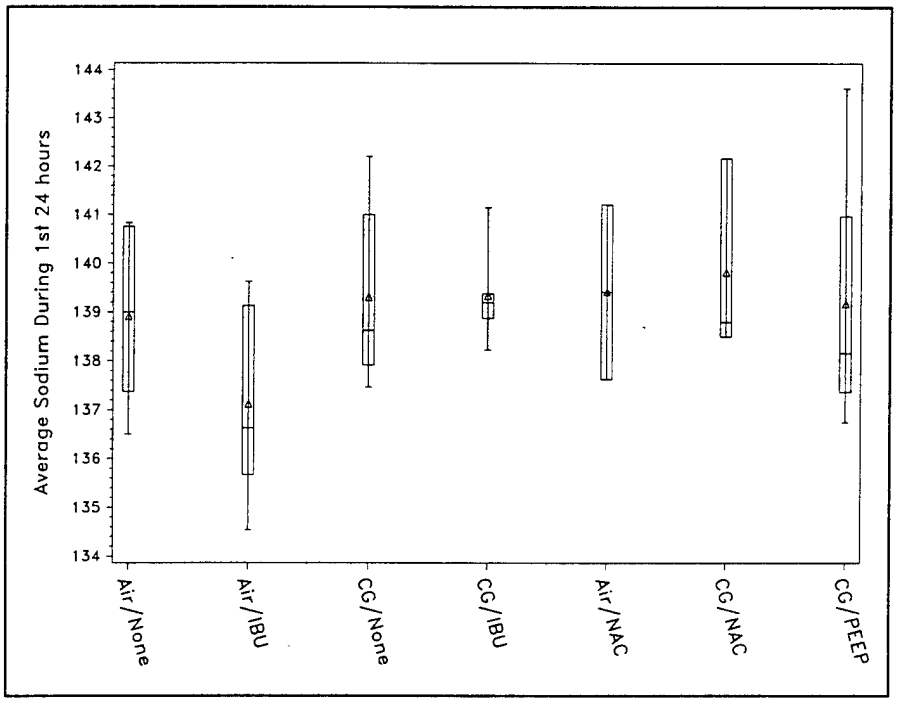


Figure B-8. Boxplots of Average Sodium Levels (mmol/L) During First 24 Hours for Seven Exposure/Treatment Groups.

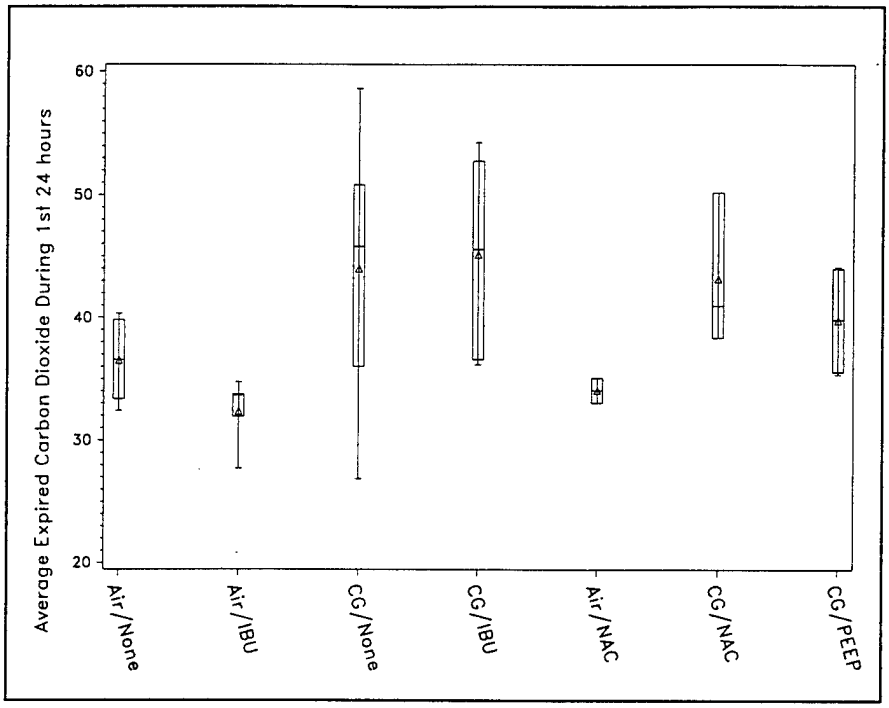


Figure B-9. Boxplots of Average Expired Carbon Dioxide (%) During First 24 Hours for Seven Exposure/Treatment Groups.

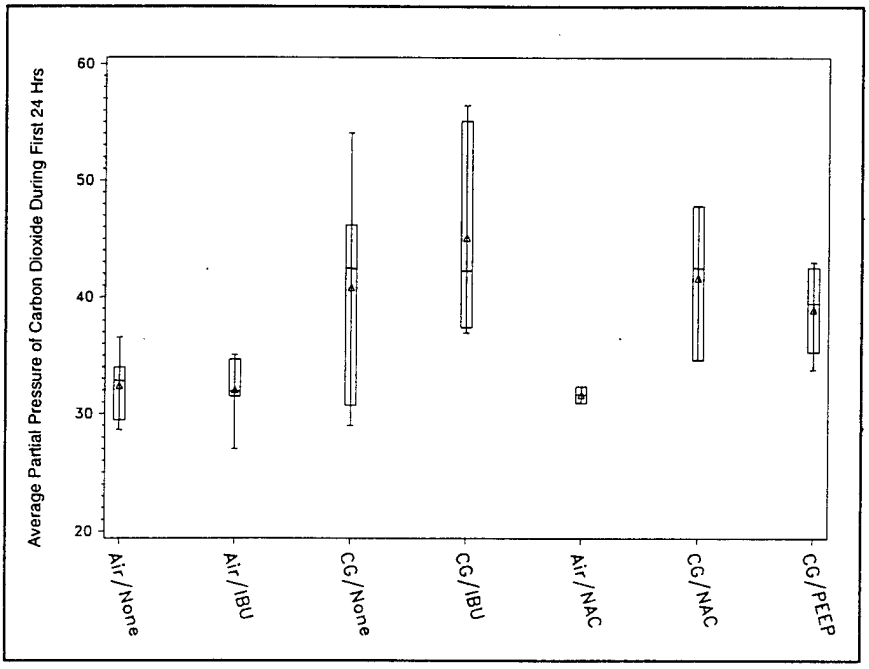


Figure B-10. Boxplots of Average Partial Pressure of Carbon Dioxide (mm Hg) During First 24 Hours for Seven Exposure/Treatment Groups.

APPENDIX C
Group Mean Plots

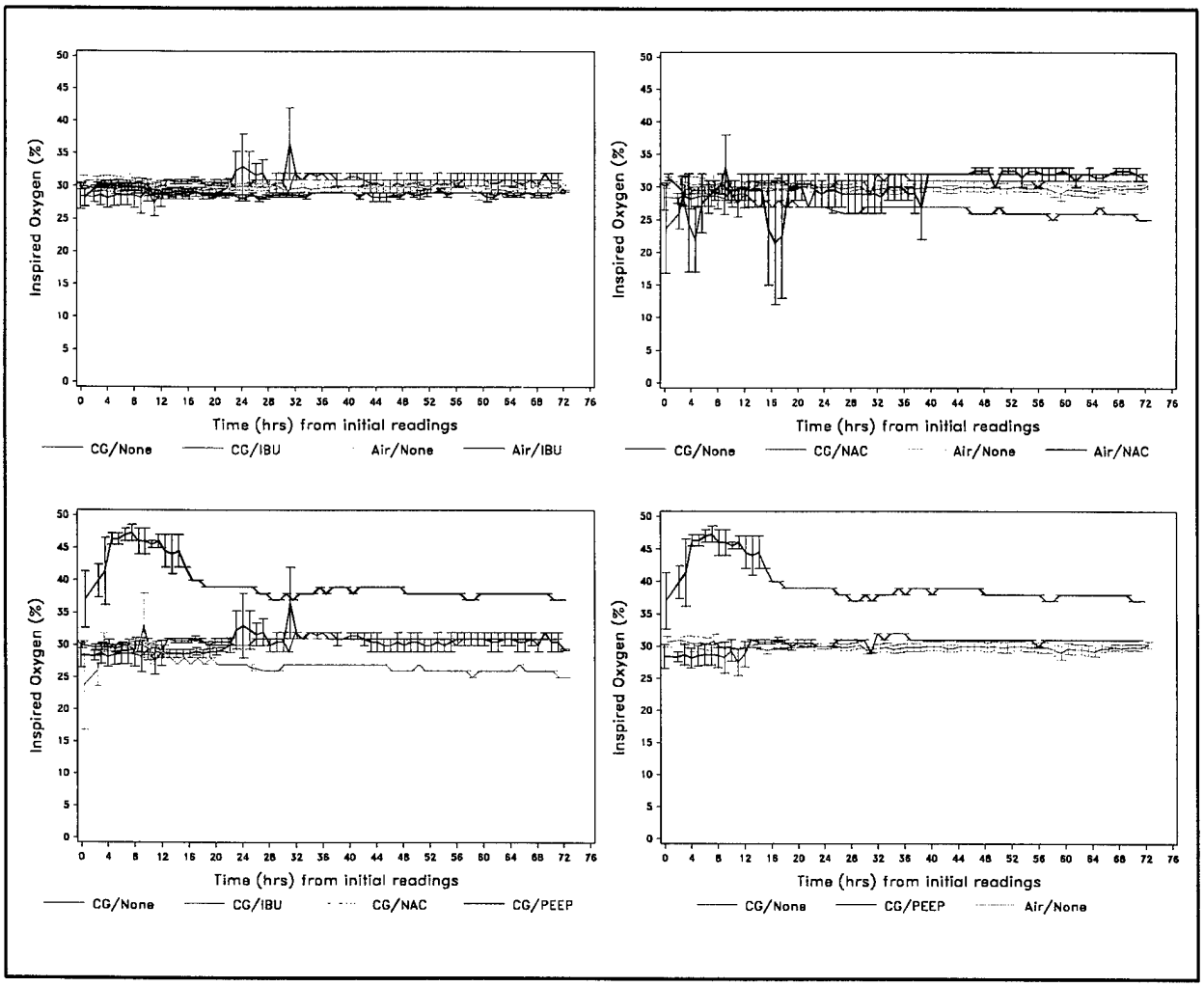


Figure C-1. Mean Scores of Inspired Oxygen for Different Sets of Exposure/Treatment Groups.

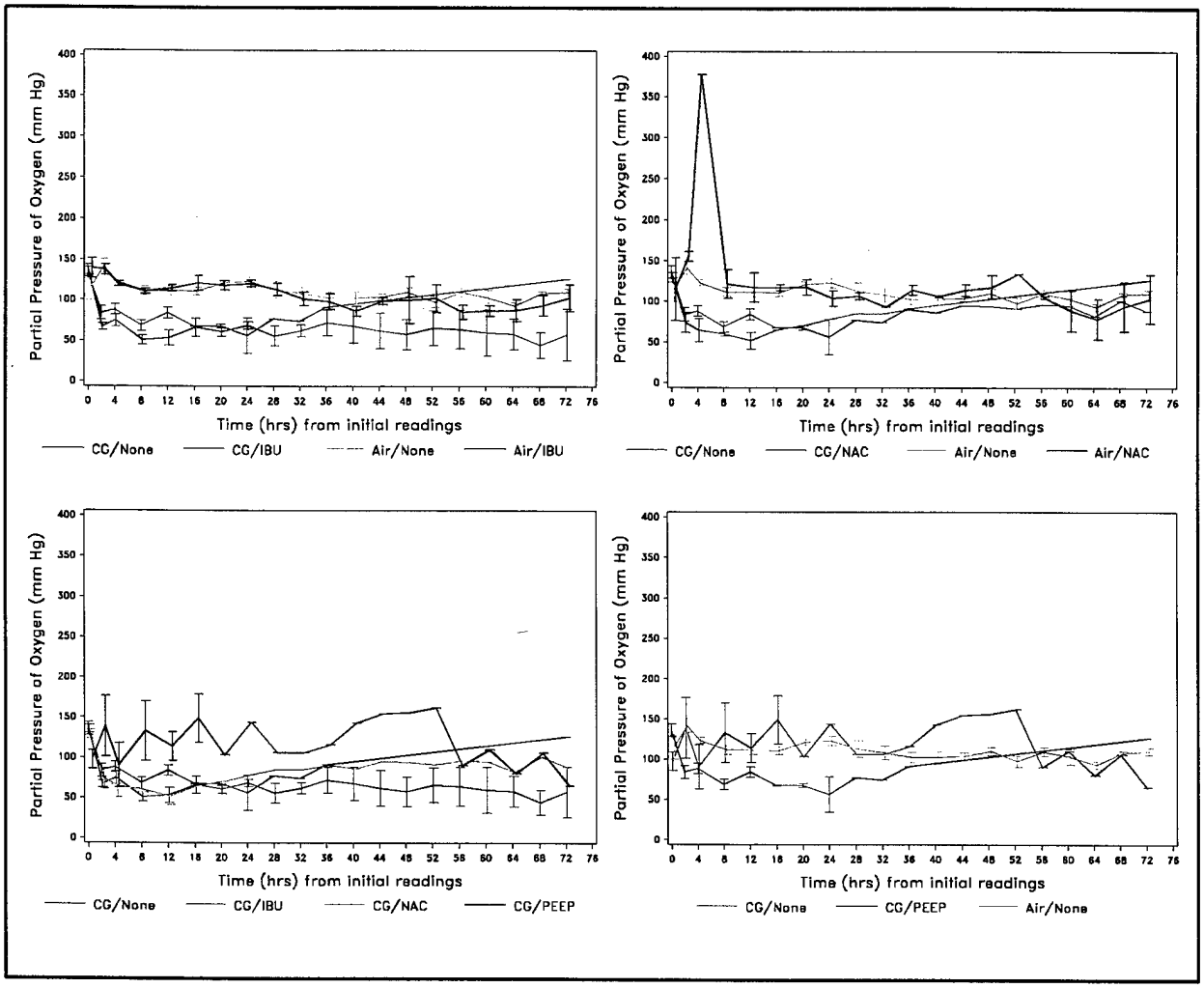


Figure C-2. Mean Scores of Arterial Partial Pressure of Oxygen for Different Sets of Exposure/Treatment Groups.

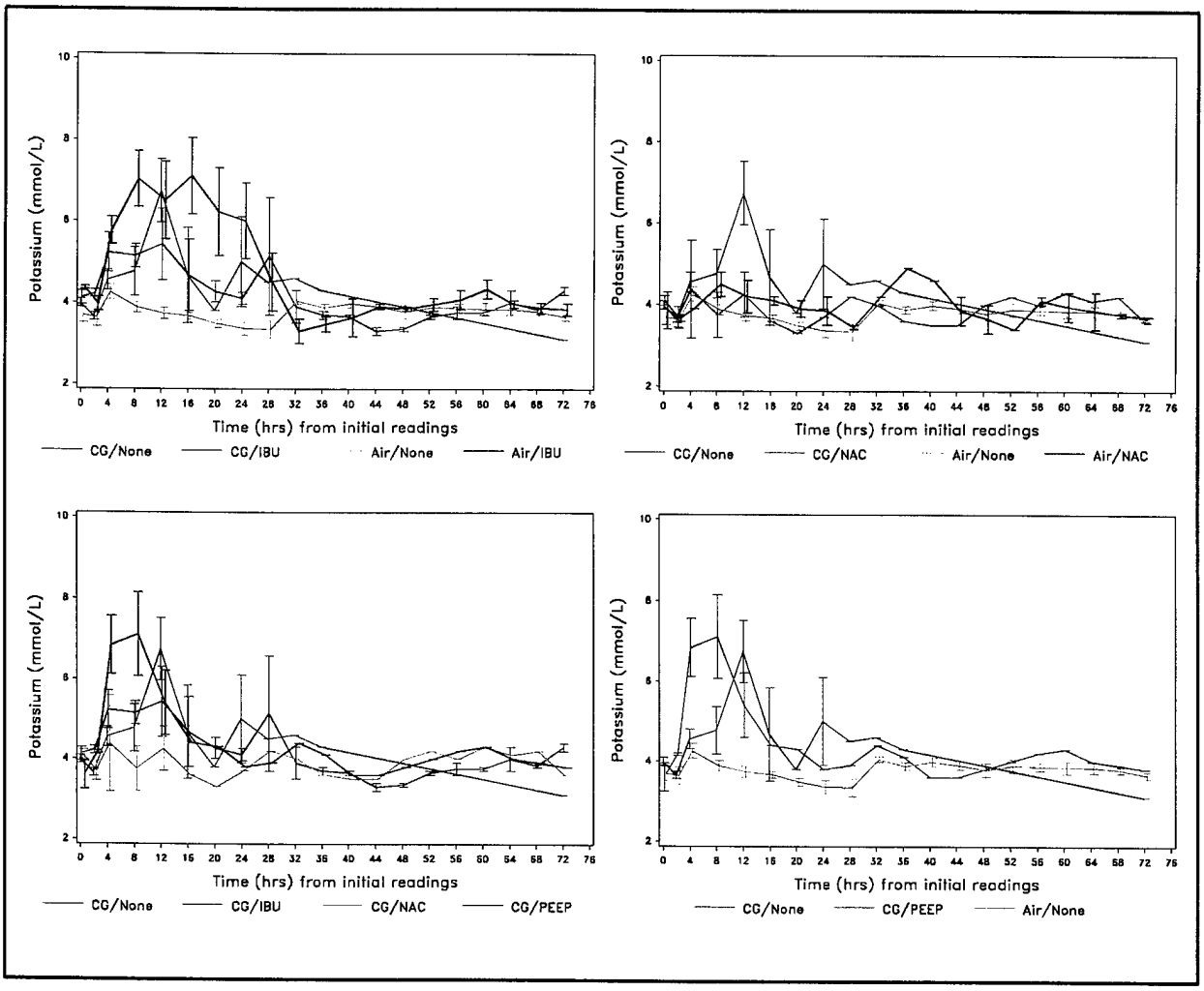


Figure C-3. Mean Scores of Potassium for Different Sets of Exposure/Treatment Groups.

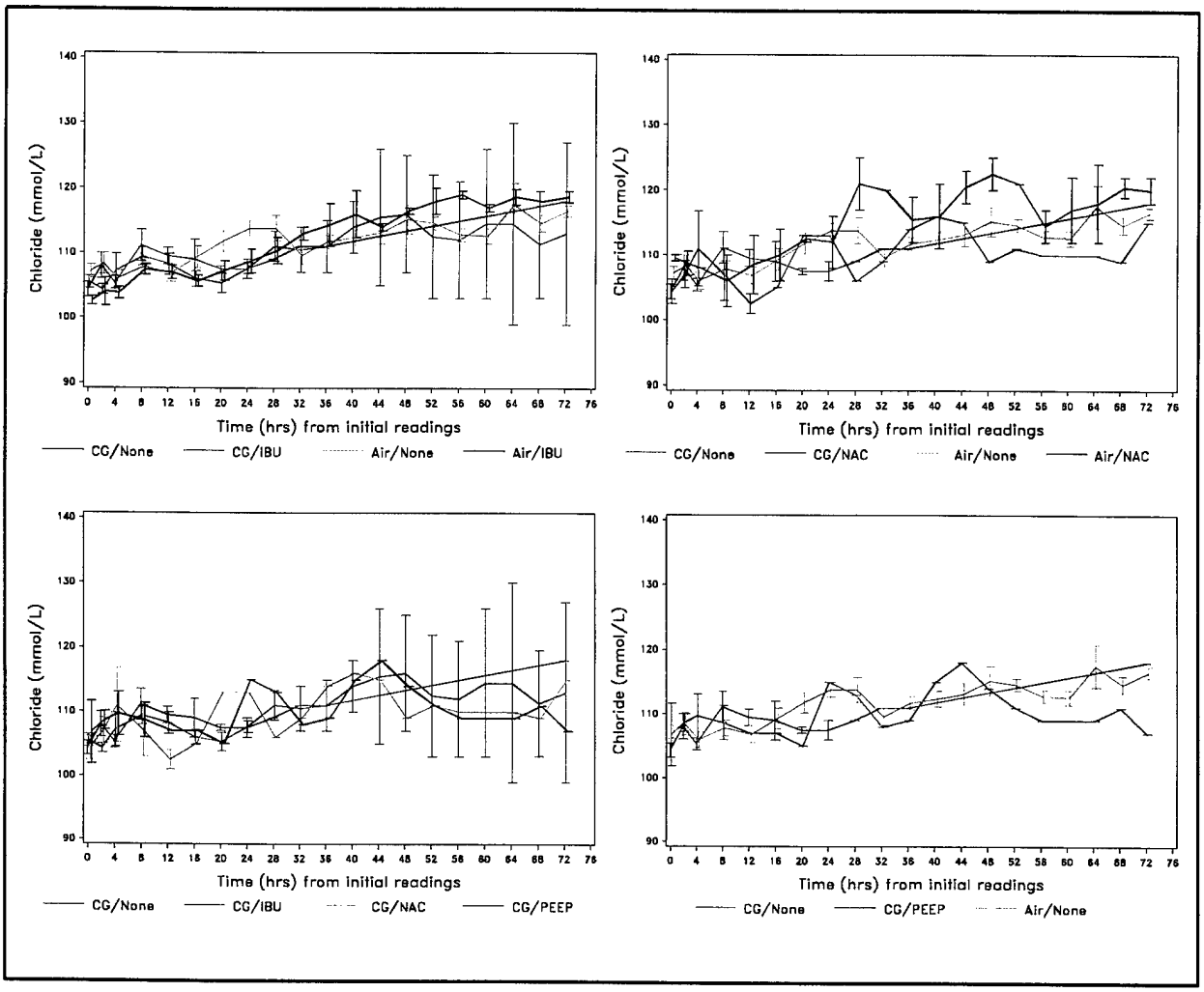


Figure C-4. Mean Scores of Chloride for Different Sets of Exposure/Treatment Groups.

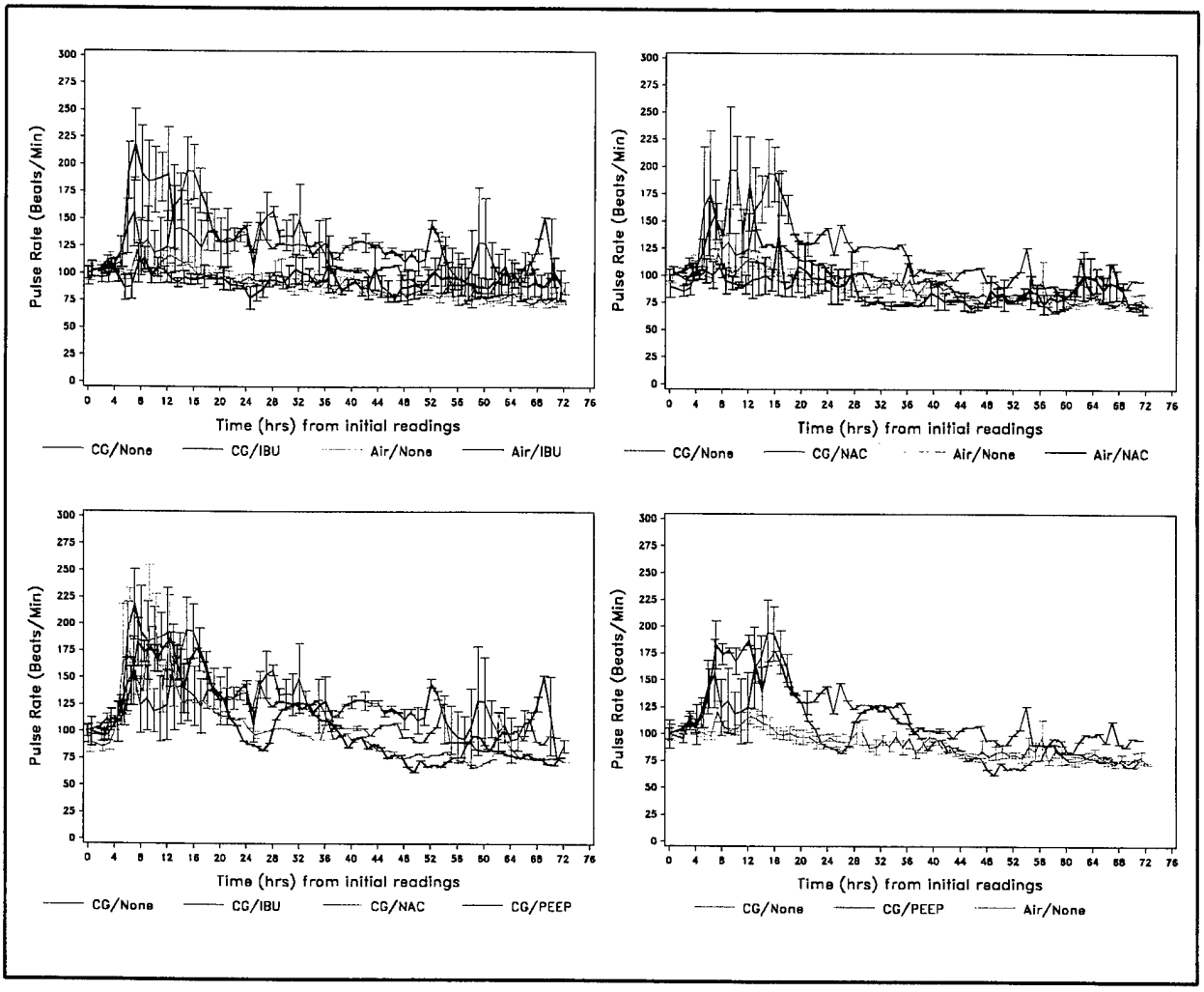


Figure C-5. Mean Scores of Pulse Rate for Different Sets of Exposure/Treatment Groups.

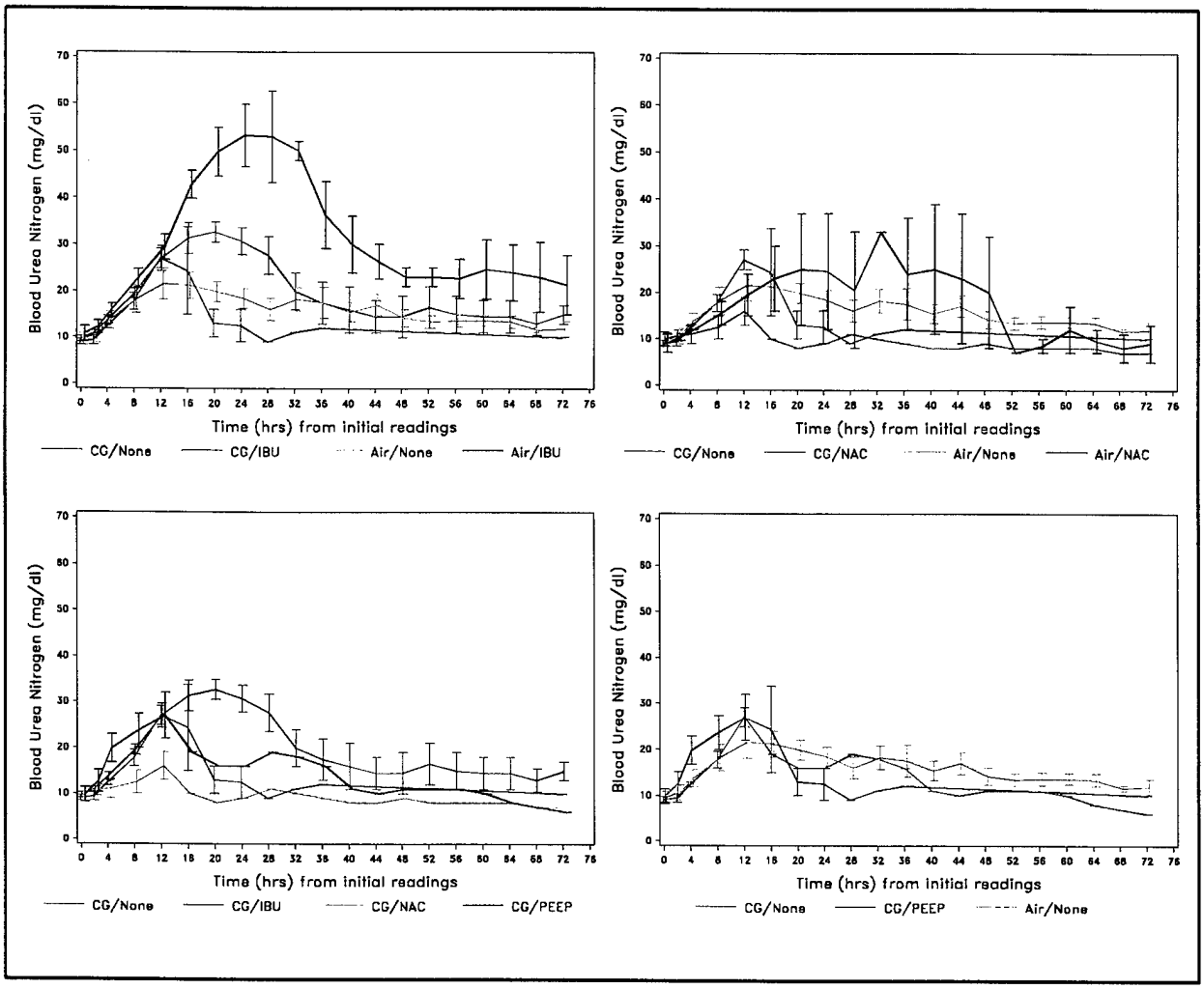


Figure C-6. Mean Scores of Blood Urea Nitrogen for Different Sets of Exposure/Treatment Groups.

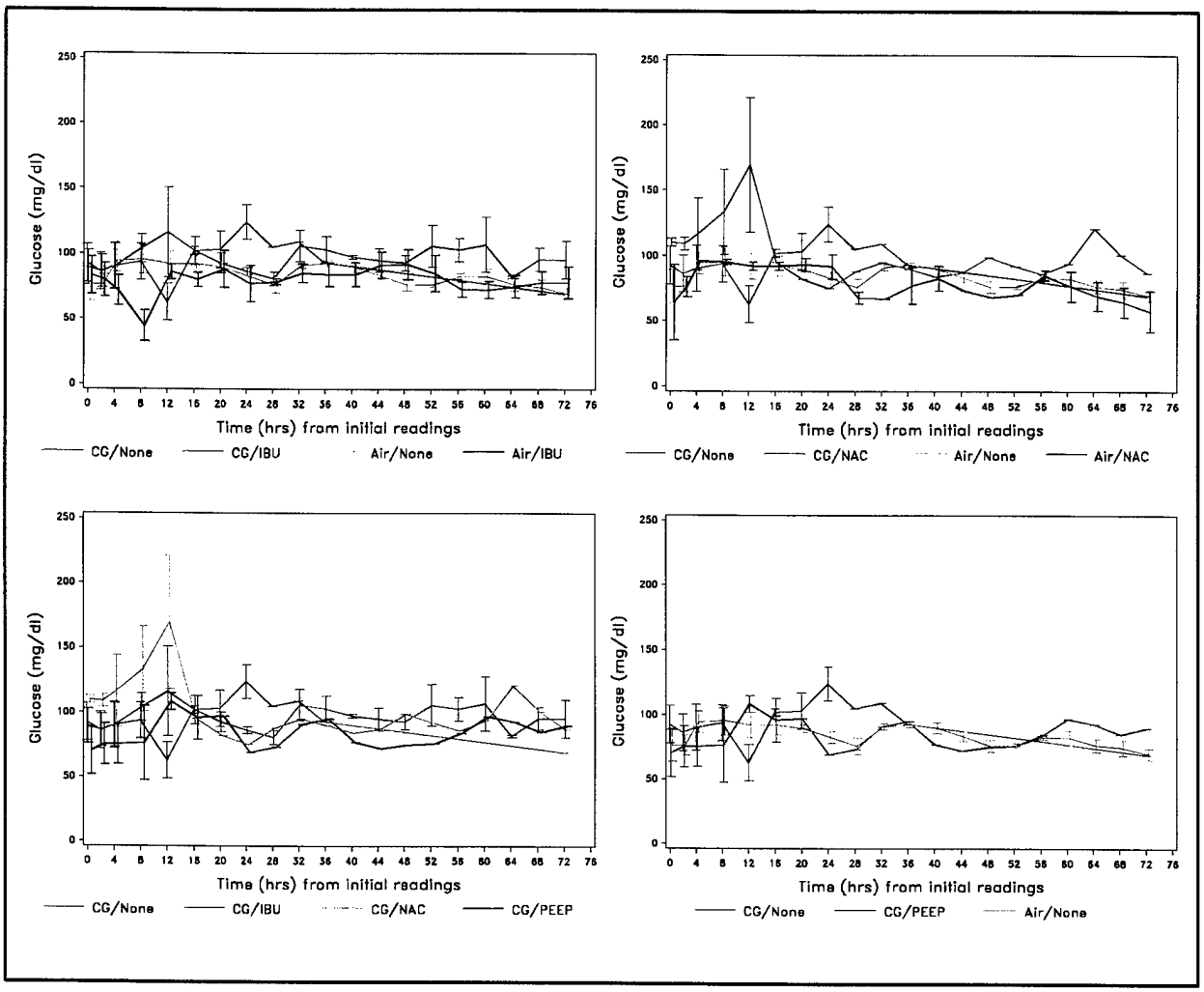


Figure C-7. Mean Scores of Glucose for Different Sets of Exposure/Treatment Groups.

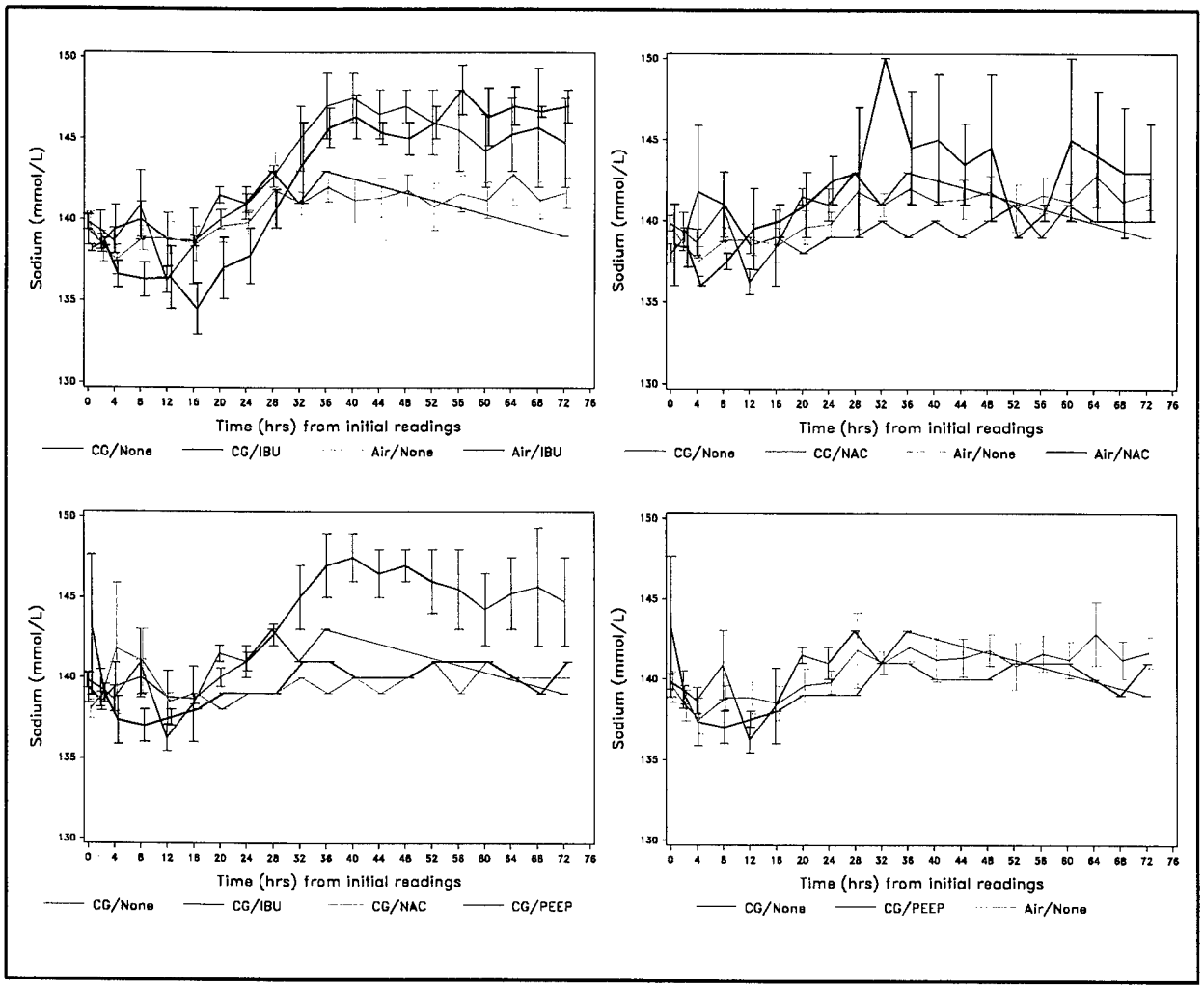


Figure C-8. Mean Scores of Sodium for Different Sets of Exposure/Treatment Groups.

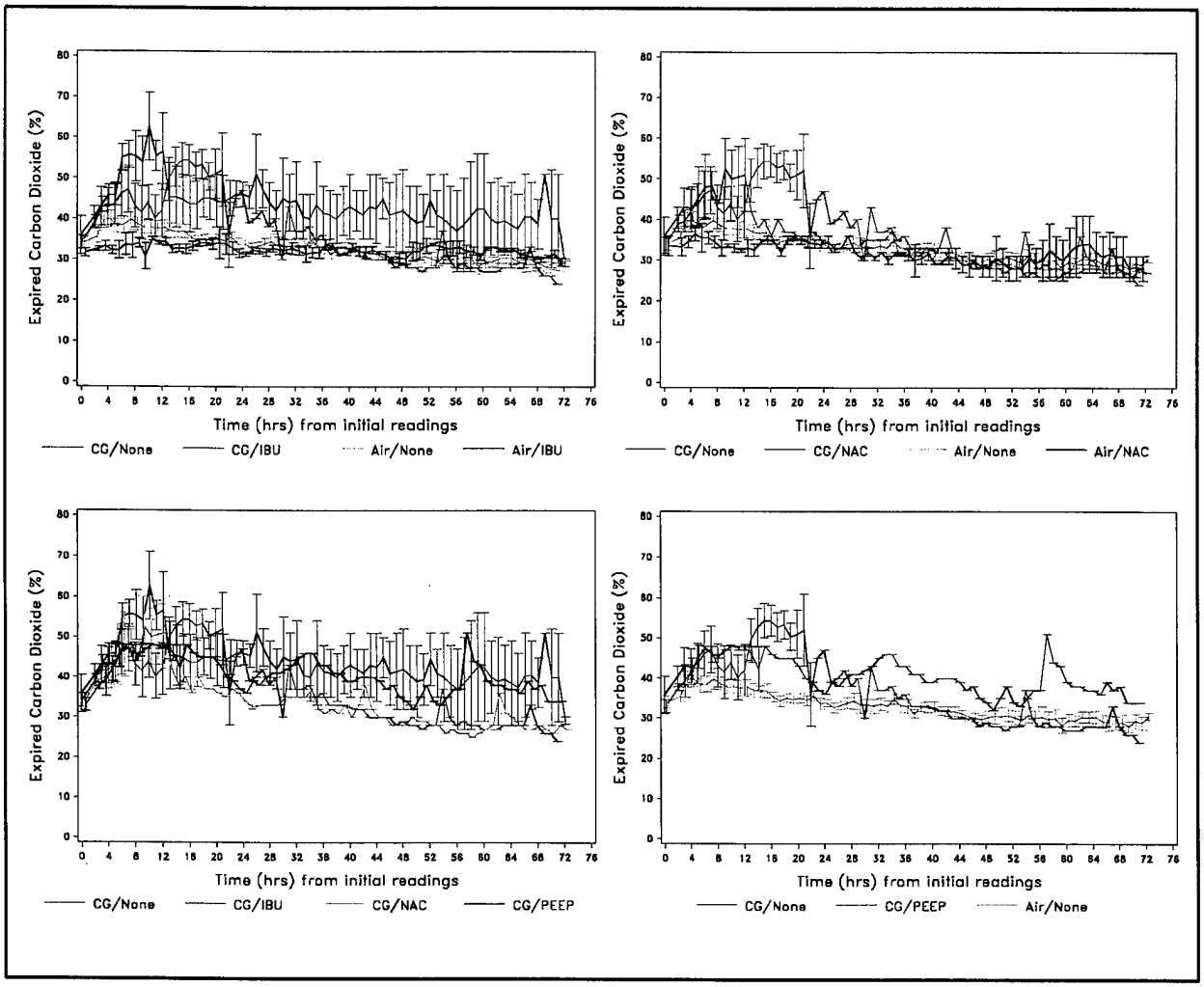


Figure C-9. Mean Scores of Expired Carbon Dioxide for Different Sets of Exposure/Treatment Groups.

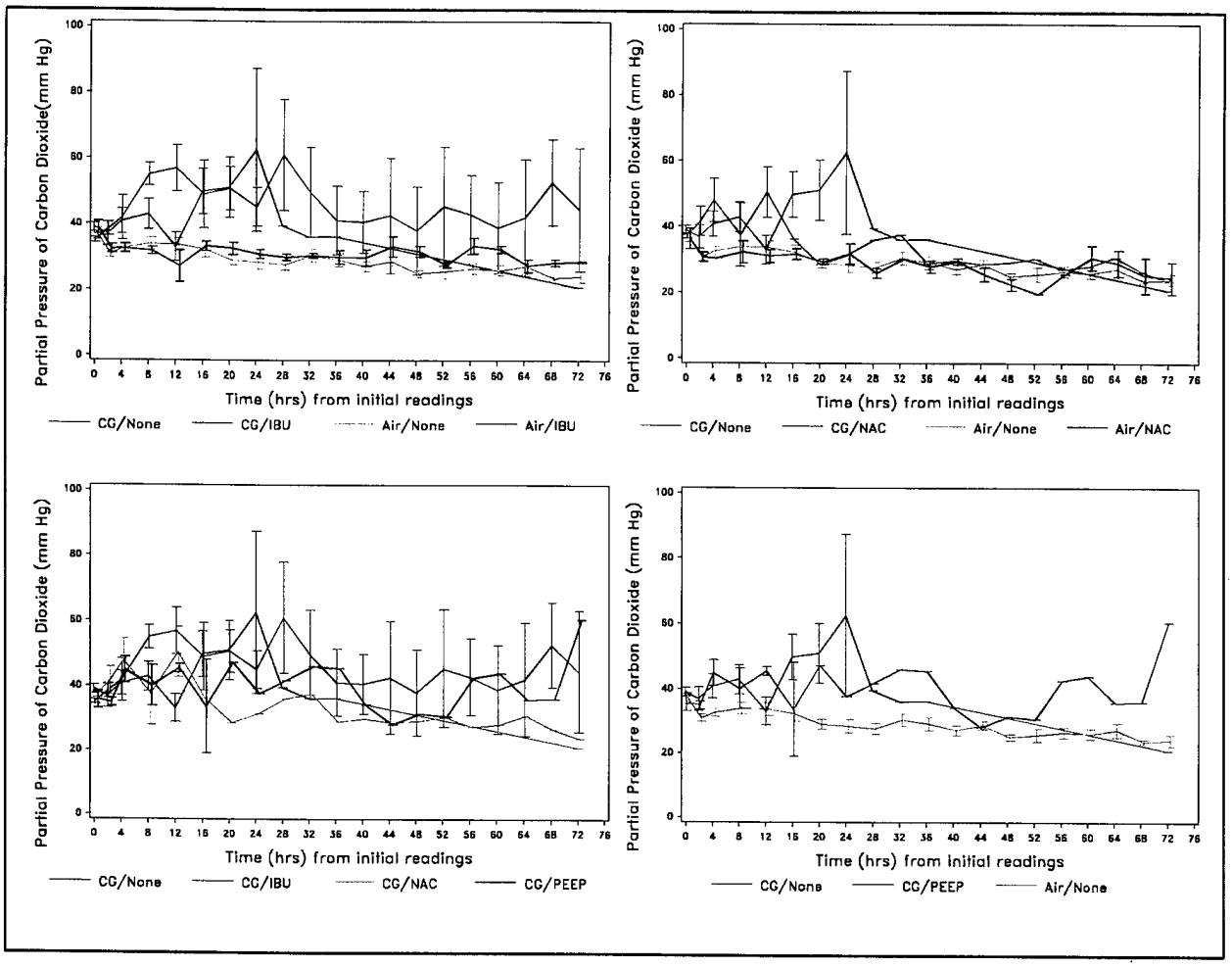


Figure C-10. Mean Scores of Partial Pressure of Carbon Dioxide for Different Sets of Exposure/Treatment Groups.

APPENDIX D: IMPEDANCE PLOTS

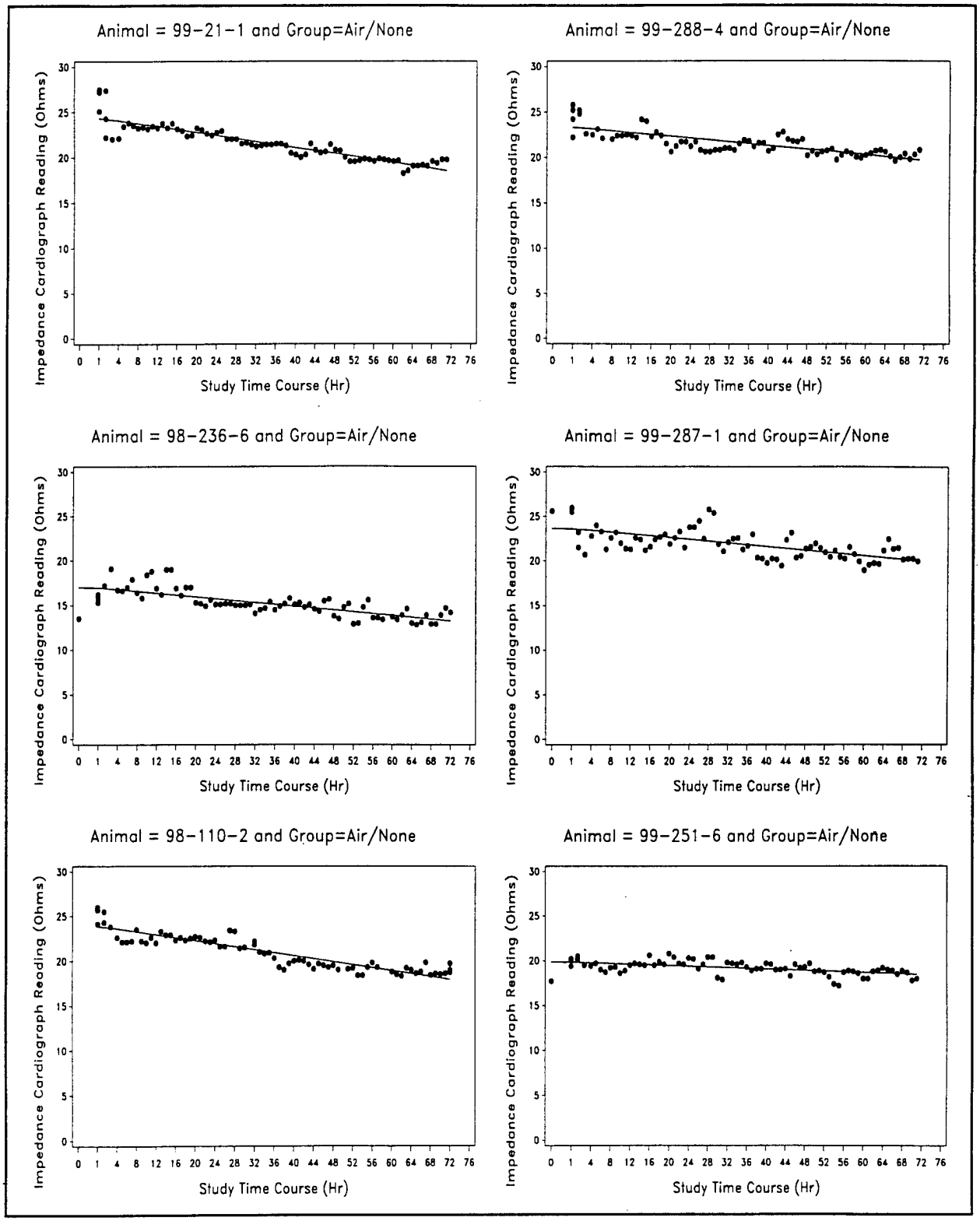


Figure D-1. Impedance Cardiograph Versus Study Timecourse with Regression Line by Animal in Air/None Group.

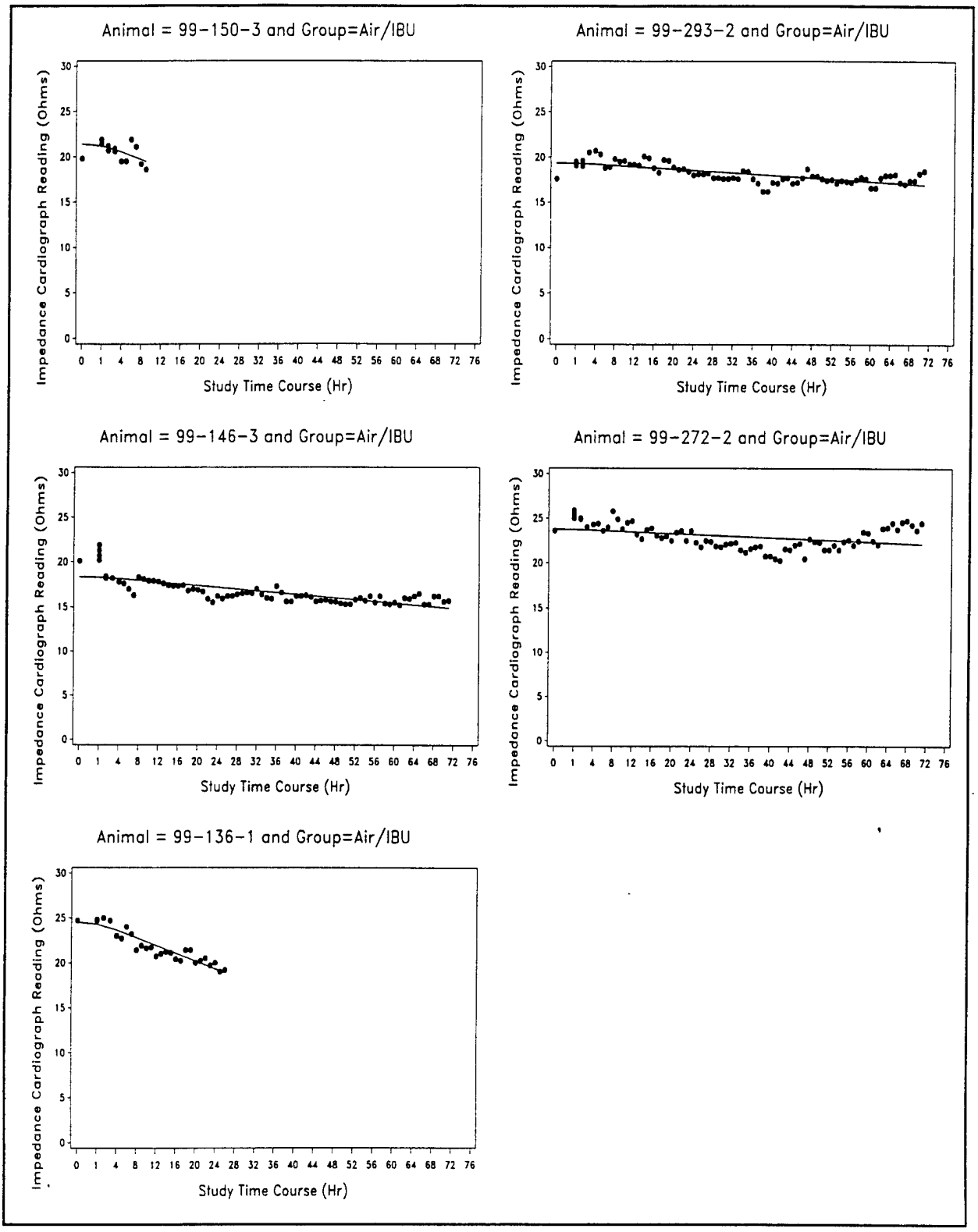


Figure D-2. Impedance Cardiograph Versus Study Timecourse with Regression Line by Animal in Air/IBU Group.

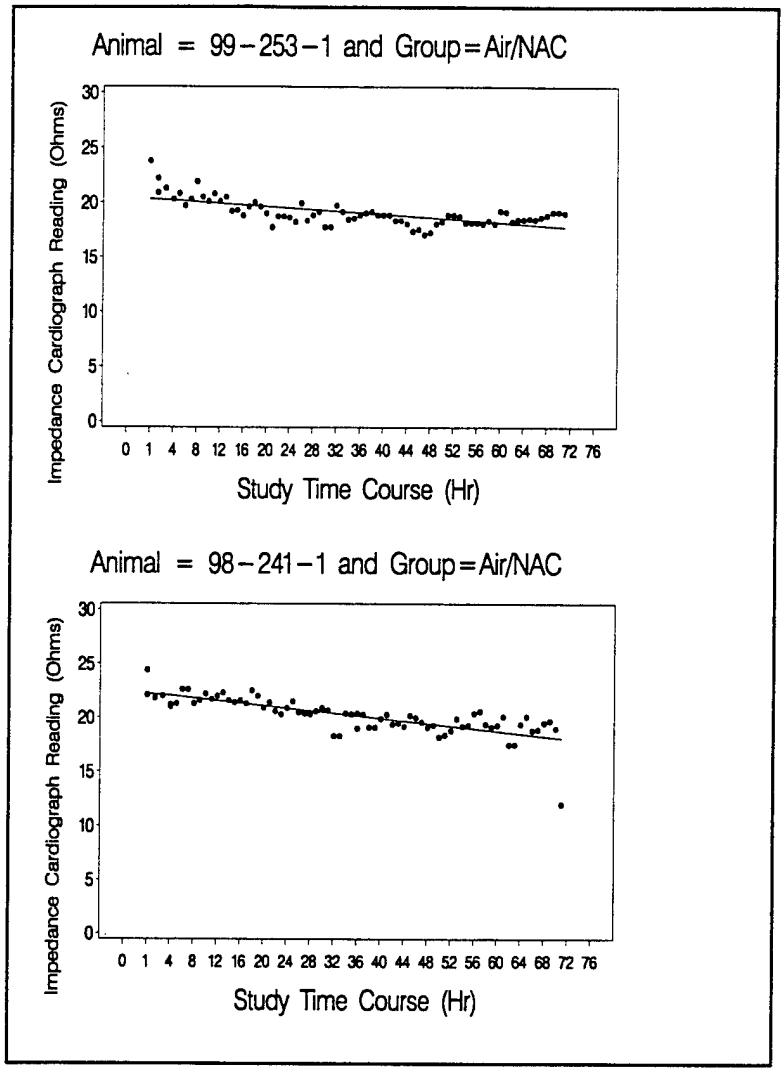


Figure D-3. Impedance Cardiograph Versus Study Timecourse with Regression Line by Animal in Air/NAC Group.

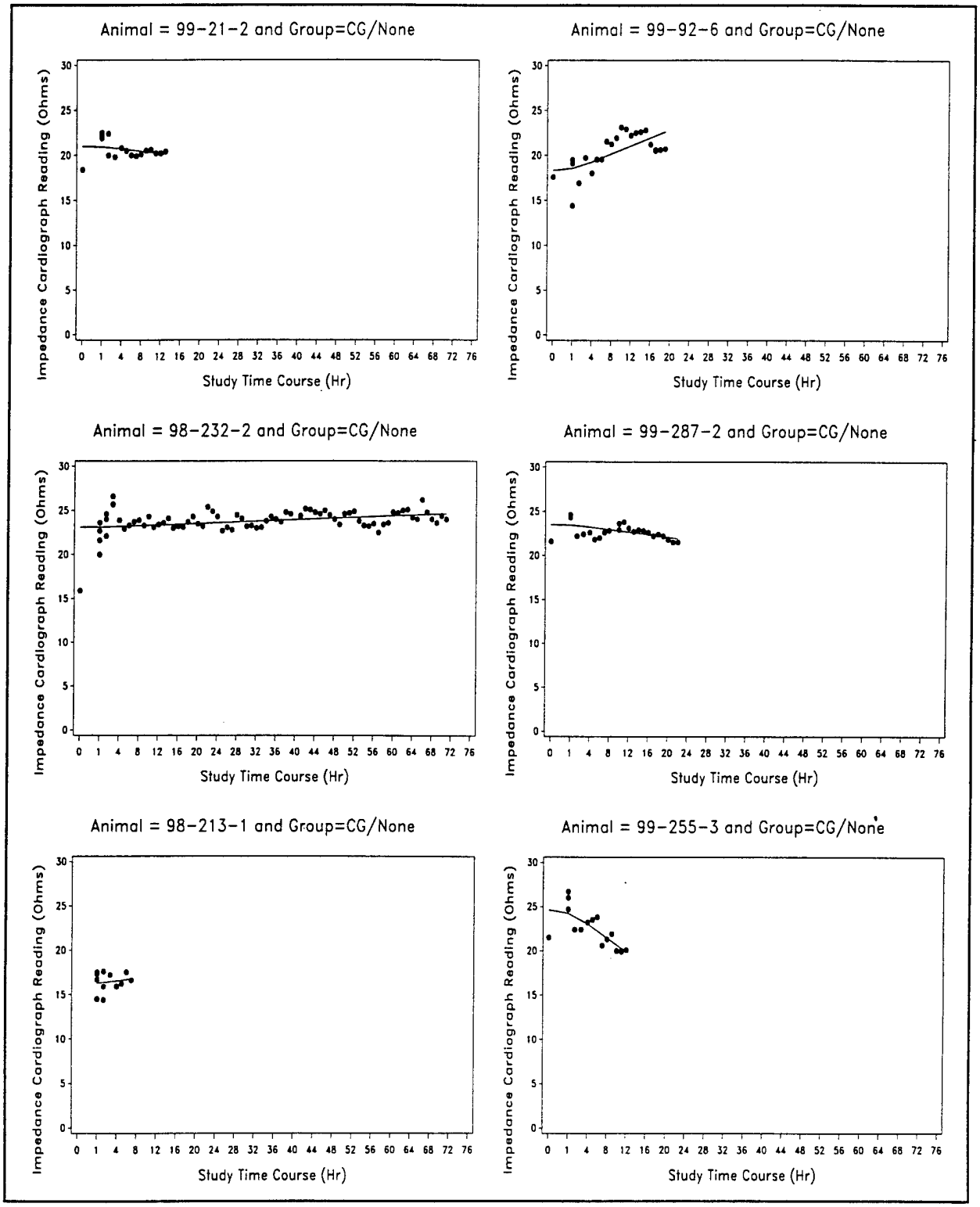


Figure D-4. Impedance Cardiograph Versus Study Timecourse with Regression Line by Animal in CG/None Group.

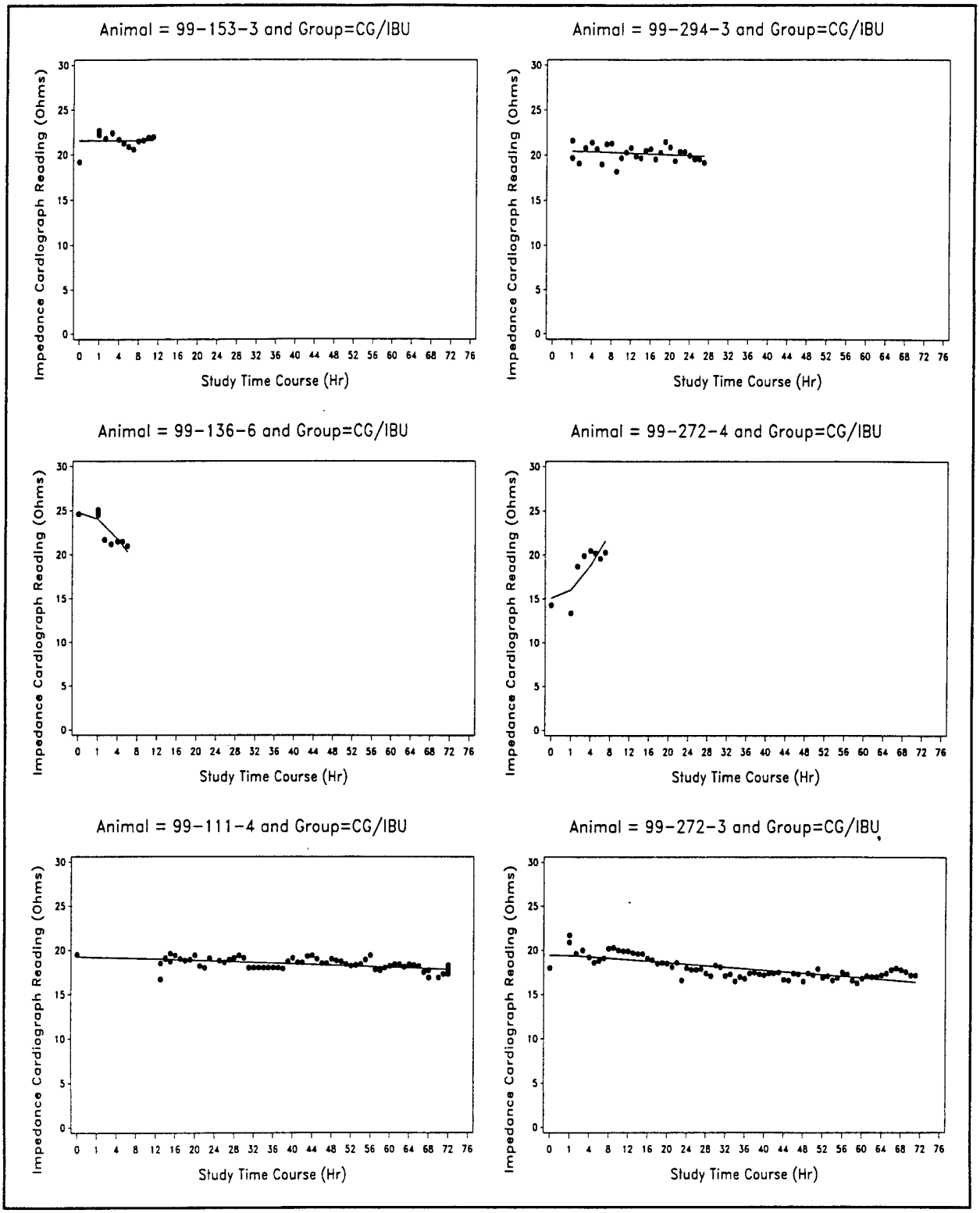


Figure D-5. Impedance Cardiograph Versus Study Timecourse with Regression Line by Animal in CG/IBU Group.

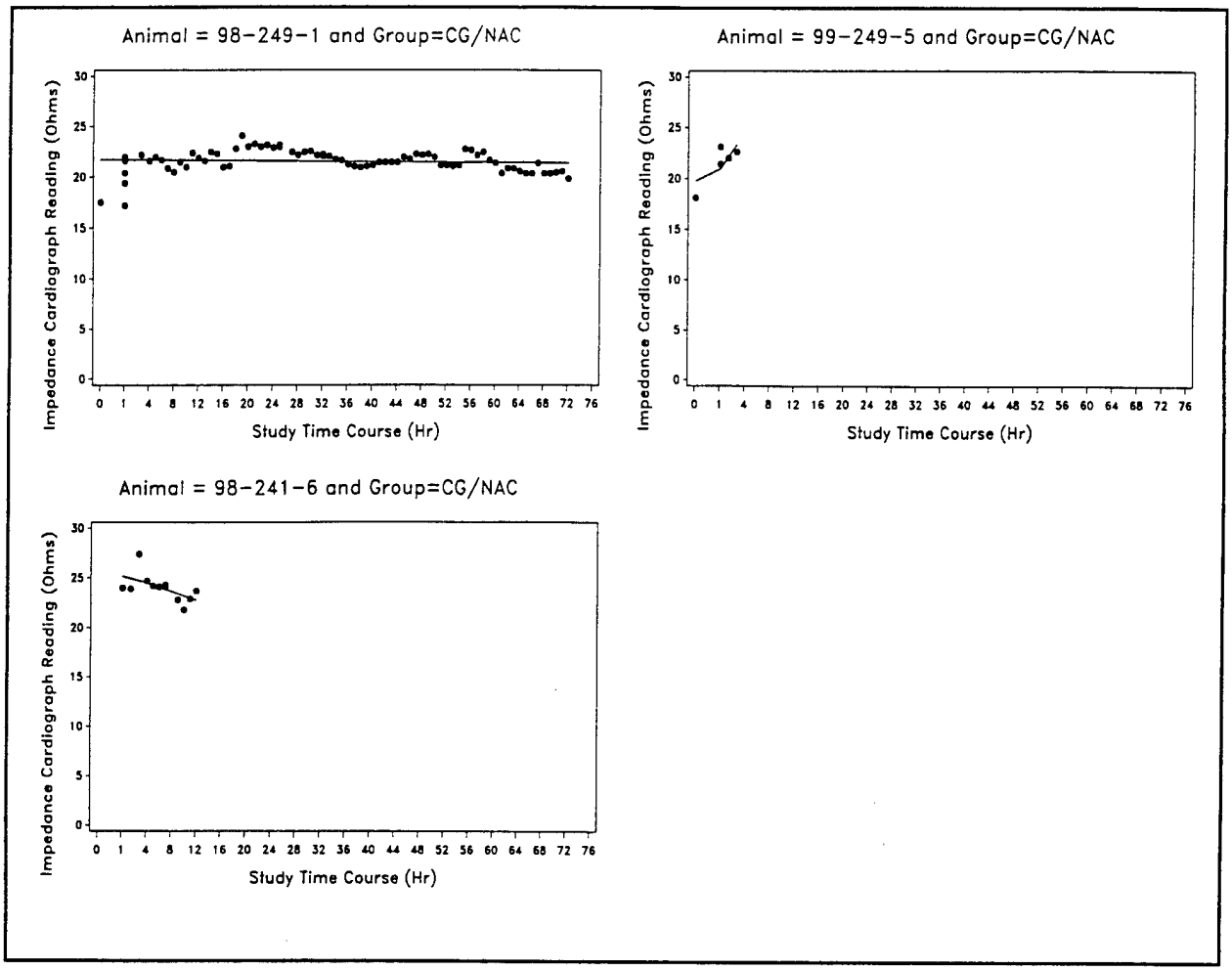


Figure D-6. Impedance Cardiograph Versus Study Timecourse with Regression Line by Animal in CG/NAC Group.

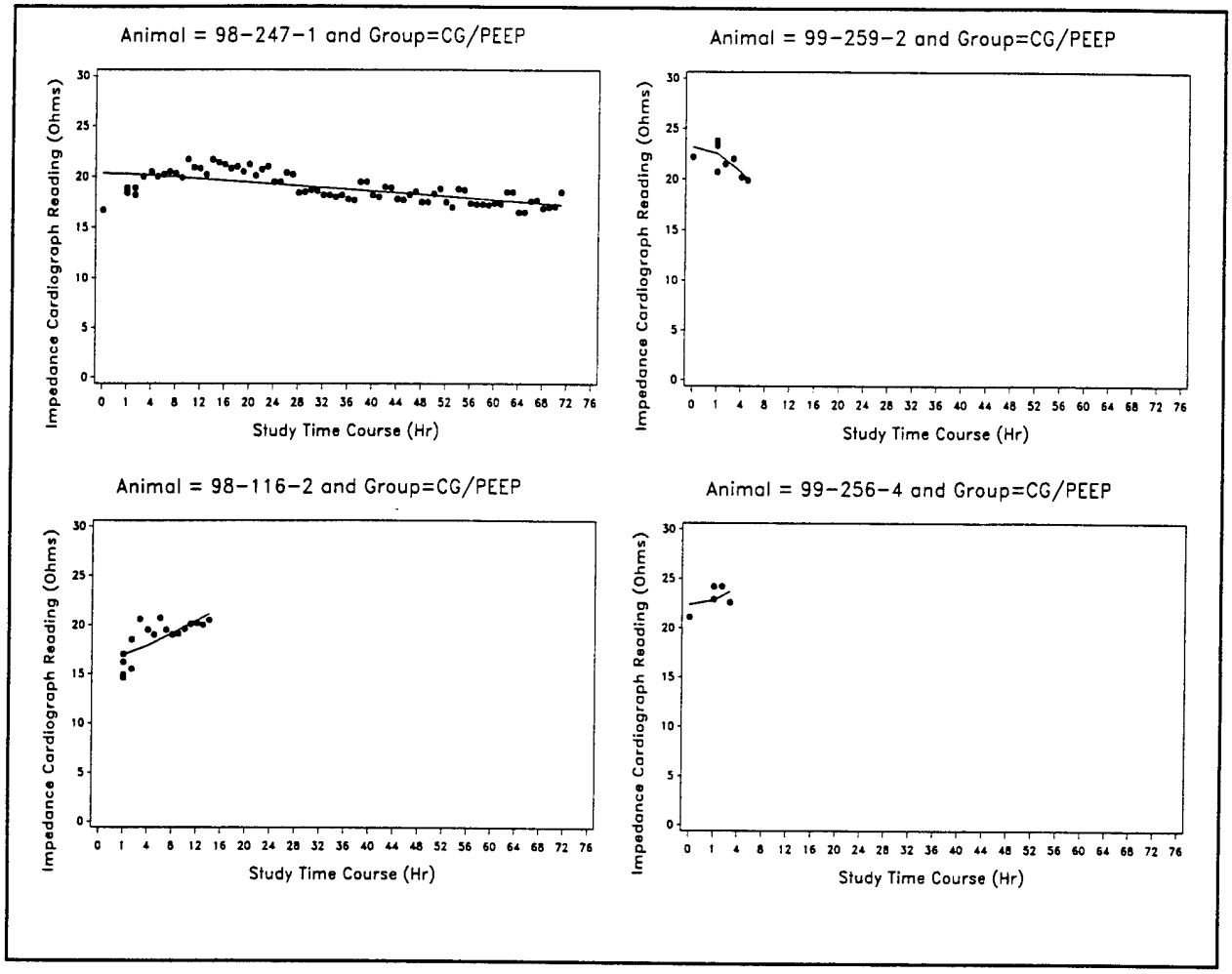


Figure D-7. Impedance Cardiograph Versus Study Timecourse with Regression Line by Animal in CG/PEEP Group.